The nature of the distribution of some risks for schizophrenia.

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The Nature Of The Distribution Of Some Risks For Schizophrenia

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Abstract

The thesis was concerned with causal factors in schizophrenia. The main question was whether some individual risk factors for schizophrenia might act throughout their range of values, or whether they showed threshold effects below which they were not associated with the illness. There was an initial discussion of concepts of schizophrenia and causation. Next, two empirical sections involved an epidemiological approach to the main question posed. These sections comprised: a clinical study in which the author collected data (The Camberwell Collaborative Psychosis Study; CCPS), and an established, general population sample (The National Survey of Health and Development; NSHD) followed prospectively. Several risk factors were reported. In the first study these were cerebral ventricle volumes, as measured by computerised tomography, in cases of schizophrenia and other psychotic illnesses, and in controls. In the NSHD the factors entailed some childhood characteristics including timing of milestones, educational achievement (I.Q.) and behaviour ratings. The children who were to suffer schizophrenia as adults were compared with those who were not.

Some approaches to analysis, such as the testing of a trend in the association between schizophrenia and a risk factor throughout its distribution, were novel in these areas. In addition to confirming the chosen factors as being associated with schizophrenia, the results suggested that they were associated with risk throughout their range, in a dose-response manner, similar to the situation in some chronic physical diseases. There was no evidence of a threshold effect for the individual risk factors studied. Such an effect would have excluded these individual factors from causing schizophrenia at sub-threshold values, requiring explanations in terms of causal heterogeneity. Such explanations being, perhaps, un-necessary, a number of implications for causal models of schizophrenia, prevention strategies and future research were feasible. These were discussed in the final chapter.

Table of Contents

Tables and Figures

Tables

Figures

Preface

Statement of authorship

The arguments developed and examined here have evolved from stimulating work with many colleagues, and from ideas prevalent in the literature regarding causation in schizophrenia and chronic physical disease. Their synthesis is my own work. The empirical work used to support this thesis comes from two large studies, both based on the work of many individuals.

The Camberwell Collaborative Psychosis Study is a wide ranging study of over two hundred people admitted to hospital due to psychotic illness, of their relatives and of a control group. It was devised by Profs. Murray, Bebbington, and Lewis, and Dr B Toone in the mid 1980s. For one year (1989/90) I managed the study, identifying and screening suitable patients, interviewing them with the Present State Examination, collecting psychological, sociodemographic and other clinical information, co-ordinating neuroimaging (CT scans) and arranging consent for further interviews of family members, particularly mothers. Additional subjects from a previous study by Dr B. Toone, Prof. P. McGuffin, Dr Ian Harvey and Mrs M. Williams are included in the CT analysis.

I collected approximately one third of the total, composite series and made operational diagnostic assessments on them all using a variety of data. I co-ordinated the final analysis of the CT brain scan images, performing over a third of the image analyses myself. Prof. Shon Lewis collected the controls. The statistical approach and analysis presented here is entirely my own work.

The MRC National Survey of Health and Development is a large, general population birth cohort which has been followed continuously since 1946, having been devised by the late Dr James Douglas who was the first Director. The scope of the study is enormous and many

people have contributed to the accumulated data. With guidance from Dr Bryan Rodgers and the current Director, Prof. Mike Wadsworth, I identified those survey members who had suffered from schizophrenia. I made operational diagnostic classifications from clinical material, some of which I collected from GPs, and from information already held by the Survey. These diagnostic classifications were made over the course of more than a year. They have been added to the permanent survey data archive and have been used by other researchers.

As was the case for the Camberwell study, the statistical analysis presented here is original in both scope and approach in this context, and is my own work. A preliminary analysis prior to all diagnostic information being assembled formed the basis of a summer project which was part of the requirements of the MSc degree in epidemiology from London University, completed in 1992. My supervisor was Prof. Michael Marmot. This work was done before the current arguments were conceived.

Two peer reviewed papers have appeared based upon the main empirical sections of this work, as set out in this thesis. These publications are:

Jones PB, Harvey I, Lewis SW, Toone BK, van Os J, Williams M & Murray RM (1994a) Cerebral ventricle dimensions as risk factors for schizophrenia and affective psychosis. An epidemiological approach to analysis. *Psychological Medicine*, 24 (4), 995-1011.

Jones PB, Rodgers B, Murray RM & Marmot MG (1994b) Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet*, 344 1398-1402.

Reprints are included at the back of the thesis. The synthesis of these two works, planned by me as the basis of my thesis, has not been published elsewhere.

Acknowledgements

Greatest thanks go to Robin Murray who stimulated and supervised the work presented in this thesis. He has provided me with many opportunities.

I am grateful to Prof. Mike Wadsworth for facilitating the investigations within the MRC National Survey of Health and Development and for giving me permission to use the data; to Dr Bryan Rodgers for his support and for sharing his ideas and detailed knowledge of the Survey; to Warren Hilder for his technical help. The past work of Dr Sheila Mann is acknowledged. Prof. Michael Marmot supervised my initial work on the survey whilst I was studying at the London School of Hygiene and Tropical Medicine. He suggested the NSHD as a sample useful for developmental work in schizophrenia and fertilised the seed of some of the ideas presented.

Many colleagues worked on the Camberwell Collaborative Psychosis Study and contributed to several years of enjoyable work. Particular thanks go to Ian Harvey, Jim van Os and Shon Lewis, partners in the dreaded CT image analysis, and to Brian Toone and again Shon Lewis for permission to use their data.

Robin Murray, Connor Duggan and Tim Croudace read a draft version of the thesis and suggested improvements. Chris Carter helped me with the figures. Errors are mine.

Structured Summary

Background

Some putative risk factors for schizophrenia have a wide range of values in the general population. For example, educational ability and the sizes of cerebral structures show continuous variation and have characteristic distributions. Values in cases of schizophrenia show considerable overlap with values in controls. In research, these continuous risk factors have often been divided into binary characteristics; present versus absent, or normal versus abnormal.

This approach makes direct, necessary and specific causal models feasible but they are not necessarily valid. Such models suggest that unaffected subjects with values of the factor below the defined threshold are not at risk of schizophrenia. They also suggest that a given factor plays no part in the causation of disorder in affected subjects with values below the threshold; other causes must be invoked. A model where risk is present throughout the range of values in a dose-response relationship is accepted in some chronic physical diseases. It does not posit aetiological heterogeneity in terms of individual risk or causal factors, although accommodates it, and also has implications for prevention strategies. Might such a model be applicable to schizophrenia?

Objective of the thesis

To investigate whether some individual putative risk factors for schizophrenia that vary continuously in the general population may confer risk throughout their range of values, or whether increased risk is occurs only above or below some threshold value.

Design

Concepts of schizophrenia, causation and risk were reviewed as a prelude to empirical investigation of these alternatives. This empirical work involved two case-control studies, within two separate samples, each investigating different factors. Schizophrenia was the condition of primary interest but findings were extended to other psychoses where possible.

The first study involved a cross-sectional survey of hospital admissions for functional psychosis, with a control group drawn from the local population and hospital staff. Cases of schizophrenia were compared with controls in terms of cerebral ventricle dimensions. The specificity of the findings regarding other psychoses was investigated. Predictions regarding these dimensions and other physical risk factors were then tested in the case groups.

The second case-control study was nested within a longitudinal investigation of a large, general population birth cohort. Survey members had been assessed regarding a variety of developmental characteristics at several points in childhood. Those with schizophrenia incident between ages 16 to 43 years were compared with the remaining population.

Setting

The cross-sectional survey, The Camberwell Collaborative Psychosis Study (CCPS), took place between 1987 and 1990. It involved three neighbouring hospitals in South London, their staff and the surrounding community.

The birth cohort was the MRC National Survey of Health and Development (NSHD), a stratified random sample of all births in the week 3-9 March 1946.

Subjects

There were 216 cases and 67 controls in the CCPS. Of the cases, 121 were classified as having RDC schizophrenia, 41 as having schizo-affective disorder, and 54 as having affective psychosis.

In the NSHD, 4176 of 5362 survey members were alive and living in the UK at age 16. Of these, 30 were identified through multiple sources as subsequently having met DSM-III-R criteria for schizophrenia or schizo-affective disorder. Controls were the remaining 4746.

Measures

In the CCPS, dimensions of cerebral ventricles, as defined by computerised tomography of the brain, were the main measures. Clinical characteristics, family history of psychiatric disorder and obstetric history were used in the subsidiary analyses of cases. In the NSHD, timing of motor and speech milestones, intelligence tests at ages 8, 11 and 15 years, and ratings of behaviour at several time points in childhood were used. The main analyses involved defining associations between schizophrenia and these items in terms of odds ratios, investigating whether there was increasing risk throughout their range, or whether there was evidence of a threshold effect.

Results

The CCPS confirmed the relationship between larger cerebral ventricle volumes and schizophrenia and other psychoses. The investigation within the NSHD confirmed the existence of a variety of differences in the development of children who subsequently developed schizophrenia, compared with their peers.

For all classes of variable in both samples, simple visual inspection of the distributions of values in the cases and controls provided no evidence of separate distributions in these two groups, or within the case group alone. For the cerebral ventricle dimensions in the CCPS, and for the IQ measures in the NSHD, there was evidence of significant linear trends in the association between these measures and risk of schizophrenia. There was no evidence of threshold effects; the larger the volumes or the lower the IQ, the greater the risk of schizophrenia in these two samples. For the structural dimensions, the results were not specific to schizophrenia. There was similar evidence of trends in associations between later schizophrenia and childhood behavioural measures in the NSHD.

Neither study had the statistical resolution to investigate multivariate risk defined in terms of several risk factors simultaneously. Nor could they investigate the precise equations best describing the risks associated with individual factors. Although the nature of the risks could be defined, albeit roughly, the proportion of variance explained by any of them was very small; if they were involved in causation, they exerted only weak or indirect effects.

Conclusions

The main argument of the thesis was supported. In terms of the individual variables examined there was no evidence of thresholds above or below which they were associated with increasing risk of schizophrenia, the main outcome of interest. There are implications for those with and those without schizophrenia. In the population, risk may be continuous. All individuals may have some degree of risk, definable in terms of individual variables, rather than some being at risk, others not. Cases did not form a dichotomy with one group showing evidence of the risk factor (e.g. enlarged ventricles) while others show none. These results were consistent with a

widespread effect, and with the majority of cases arising from the majority of the population who were at only moderate risk. Such a model incorporates complex constellations of causes, as currently accepted in some physical diseases.

Future prevention strategies might usefully target the majority at medium risk rather than the high risk minority. Given the lack of specificity of the evidence, from within and without this investigation, and the nature of possible interventions, the danger of a prevention paradox would be low. Future studies must be designed to investigate, and exclude, multivariate risk which may behave differently from the individual factors studied in this thesis.

Chapter 1

Concepts of schizophrenia, of causes and of risks

Introduction

This thesis[1] is concerned with the cause of schizophrenia, as yet unknown. It does not seek to identify any new ones but considers some of the ways in which a putative cause or causes might act, when and in whom. It examines a number of factors which have been mooted as related to, or manifestations of, possible causes of schizophrenia. These are the dimensions of cerebral ventricles in adults with the disorder, and early childhood development, IQ and behaviour, in children who are destined to suffer from it. The nature of the associations between each of these factors and schizophrenia is investigated in an attempt to examine the argument that none represents a direct, one-to-one causal relationship in all, or a sub-group, of the disorder.

Several conventional risk factors for schizophrenia, explained hitherto as being applicable to only a minority of the disorder, may be better understood as continuous risk factors influencing many cases, perhaps the majority. In contrast to the situation where discrete, categorical events act as sufficient causes for an aetiological subgroup of schizophrenia, the effects of some possible causes, or of markers of causes, may be widespread.

Many hypotheses arise from this argument. The most direct is that a model where these characteristics represent continuous risk factors within the population better describes any empirical observations of their association with schizophrenia than does a model concerned with categorical, all or nothing events. As a background the concepts of schizophrenia and of causes are described and discussed, relatively briefly as both represent centuries of thought. Terms such as risk are defined. I conclude that schizophrenia is a diverse clinical syndrome, justifying the diverse risk factors which are used to examine the argument set out in the

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[1] The term *Thesis* denotes this written account of the theoretical and empirical examination of a number of arguments. Those arguments, to which the term could also apply, are set out in the following paragraphs and in Chapter 2.

previous paragraph. Some of the problems with concepts of causation in relation to chronic physical diseases are highlighted with respect to schizophrenia. The argument is then examined under two sets of conditions within two separate, empirical studies. Its consequences are discussed in two ways. First, regarding these two specific studies and second, in wider terms regarding causal and possibly preventative models of schizophrenia.

The two empirical studies are considered in Chapters 3 and 4, respectively. The first one is a structural neuroimaging study of adults admitted to hospital because of functional psychosis. The second is a large, general population birth cohort with longitudinal information on neurodevelopment, intelligence and social behaviour of children, some of whom developed schizophrenia in adult life. In both studies, the initial approach is to examine whether categorical definitions of abnormality in these characteristics are associated with schizophrenia. This approach is then contrasted with a search for linear associations between risk of schizophrenia and continuous measures of these characteristics when there has been no attempt to define them in terms of normal or abnormal values.

The main argument of the thesis is that the categorisation of putative causes as either present or absent which is inherent in the former approach is both unnecessary and has less explanatory power than the latter, dimensional view. Despite being in accord with many traditional views on disease causation, the continued use of categorical models has resulted in some spurious conundrums in the literature. In particular, the overlap between case and control values for virtually everything which has been mooted as being important in aetiological research.

What is schizophrenia?

For contemporary research and for the purposes of this thesis, schizophrenia is a clinical syndrome of psychosis, as defined in current operational definitions. There is no single most valid definition (Andreasen, 1995). The two different definitions used in the two empirical sections of this thesis, the revised third edition of the Diagnostic and Statistical Manual (DSM-III-R) of the American Psychiatric Association (APA, 1987) and the Research Diagnostic Criteria (RDC) devised by Spitzer et al., (1978), have been chosen because of their wide applicability. The diagnostic criteria are shown overleaf in Table 1.1 a & b. These are cases of schizophrenia for the purposes of this thesis, as used in epidemiology and other research.

Other diagnostic categories are mentioned in the thesis, such as affective psychosis and schizo-affective disorder. The criteria defining these categories are not presented but have a similar, menu structure (Spitzer et al., 1978; APA, 1987).

As yet there is no accepted aetiological classification of schizophrenia, often seen as the pinnacle of nosology (Susser, 1973), although suggestions have been made (e.g. Murray et al., 1985). The disorder exists merely as a clinical syndrome of these symptoms and signs which is generally useful and which is evolving (Kendell, 1972; Zubin & Spring, 1977; Clare, 1980).

Table 1.1A Research Diagnostic Criteria (RDC) for Schizophrenia

A through C are required for the period of illness being considered.

A. During an active phase of the illness (may or may not now be present) at least two of the following are required for definite and one for probable:

1) Thought broadcasting, insertion, or withdrawal.
2) Delusions of being controlled (or influenced), other bizarre delusions, or multiple delusions.
3) Somatic, grandiose, religious, nihilistic, or other delusions without persecutory or jealous content lasting at least one week.
4) Delusions of any type if accompanied by hallucinations of any type for at least one week.
5) Auditory hallucinations in which either a voice keeps up a running commentary on the subject's behaviours or thoughts as they occur, or two or more voices converse with each other.
6) Non-affective verbal hallucinations spoken to the subject.
7) Hallucinations of any type throughout the day for several days or intermittently for at least one month.
8) Definite instances of marked formal thought disorder accompanied by either blunted or inappropriate affect, delusions or hallucinations of any type, or grossly disorganised behaviour.

B. Signs of the illness have lasted at least two weeks from the onset of a noticeable change in the subject's usual condition (current signs of the illness may not now meet criterion A and may be residual symptoms only, such extreme social withdrawal, blunted or inappropriate affect, mild formal thought disorder, or unusual thoughts or perceptual experiences).

C. At no time during the active period (delusions, hallucinations, marked formal thought disorder, bizarre behaviour etc.) of illness being considered did the subject meet the full criteria for either probable or definite manic or depressive syndrome (criteria a and B under Major Depressive or Manic Disorders) to such a degree that it was a prominent part of the illness.

Subjects with a full depressive or manic syndrome which overlaps active psychotic symptoms are excluded and are diagnosed as either Schizo-affective Disorder, Major Depressive Disorder, or Manic Disorder. If the symptoms in A occur only during periods of alcohol or drug use or withdrawal from them, the diagnosis should be Other Psychiatric Disorder because of the likely organic Aetiology of the symptoms.

Table 1.1b DSM-III-R Diagnostic criteria for a Schizophrenia Disorder

A. Presence of characteristic psychotic symptoms in the active phase: either (1), (2) or (3) for at least one week (unless the symptoms are successfully treated):

1. Two of the following:
   (a) delusions
   (b) prominent hallucinations (throughout the day for several days or several times a week for several weeks, each hallucinatory experience not being limited to a few brief moments).
   (c) incoherence or marked loosening of associations
   (d) catatonic behaviour
   (e) flat or grossly inappropriate affect

2. bizarre delusions involving a phenomenon that the person's culture would regard as totally implausible (e.g. thought broadcasting, being controlled by a dead person).

3. prominent hallucinations [as defined in 1(b) above] of a voice with content having no apparent relation to depression or elation, or a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other.

B. During the course of the disturbance, functioning in such areas as work, social relations, and self-care is markedly below the highest level achieved before onset of the disturbance (or, when the onset is in childhood or adolescence, failure to achieve expected level of social development).

C. Schizoaffective disorder and mood disorder with psychotic features have been ruled out, i.e., if a major depressive or manic syndrome has ever been present during an active phase of the disturbance, the total duration of all episodes of a mood syndrome has been brief relative to the total duration of the active and residual phases of the disturbance.

D. Continuous signs of the disturbance for at least six months. The six-month period must include an active phase (of at least one week, or less if symptoms have been successfully treated) during which there were psychotic symptoms characteristic of schizophrenia (symptoms in A.), with or without a prodromal or residual phase, as defined below.

Prodromal phase: A clear deterioration in functioning before the active phase of the disturbance that is not due to a disturbance in mood or to a psychoactive substance use disorder and that involves at least two of the symptoms listed below.

Residual phase: Following the active phase of the disturbance, persistence of at least two of the symptoms noted blow, these not being due to a disturbance in mood or to a psychoactive substance use disorder.

Prodromal or residual symptoms:

1. marked social isolation or withdrawal
2. marked impairment in role functioning as wage-earner, student, or homemaker
3. markedly peculiar behaviour (e.g., collecting garbage, talking to self in public, hoarding food)
4. marked impairment in personal hygiene and grooming
5. blunted or inappropriate affect
6. digressive, vague, over elaborate, circumstantial speech, or poverty of speech, or poverty of content of speech
7. odd beliefs or magical thinking, influencing behaviour and inconsistent with cultural norms (e.g., superstitiousness, belief in clairvoyance, telepathy, "sixth sense", "others can feel my feelings", overvalued ideas, ideas of reference)
8. unusual perceptual experiences (e.g. recurrent illusions, sensing the presence/force of absent person)
9. marked lack of initiative, interests of energy

E. It cannot be established that an organic factor initiated and maintained the disturbance.

F. If there is a history of autistic disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present.

As a "functional" psychosis, the syndrome is often defined as being without cause, or at least one thought of as acting on the brain rather than the psyche (Lewis, 1995). Known causes of the syndrome such as some drugs and epilepsies lead to a diagnosis being excluded in contemporary classifications including the two used here, and in the most recent major classifications used for research; namely, DSM-IV (American Psychiatric Association, 1994) and the International Classification of Diseases 10th Edition (World Health Organisation, 1993).

The deleterious effect that this persistence of a Cartesian mind-body split may have on the search for the causes of schizophrenia is well recognised (Murray et al., 1985; Ron & Harvey, 1990). It does not rest easily with contemporary, neurobiological formulations of the mechanisms of normal and abnormal mental phenomena. I do not wish to explore the reductionist argument (Guze, 1989) but I consider that a current explanation of any psychological event cannot be thought of as complete unless brain function (or dysfunction) is included. However, an incomplete explanation can still be a useful one, and can be considered in parallel with other partial models.

Some features of the schizophrenia syndrome are recognisable in classical Greek literature (Bynum, 1983) when they were considered to be separate from the agitations or manic states which were accompanied by fever; the phrenitides. This is similar to the distinction, mentioned above, that some still make today between functional and organic psychosis. Keeping at a clinical level, it was during the 19th century that nosologists and physicians began to group together these syndromes not associated with manifest organic states (such as neurosyphilis) into distinct disorders. Kraepelin is widely credited with the first description of what would today be recognised as schizophrenia (Murray, 1994). He used the term "dementia praecox" to subsume the syndromes of catatonia, hebephrenia, and dementia paranoides into a single entity

within the functional, "endogenous" psychoses. Kraepelin distinguished this group from manic depression and from the dementia associated with old age, which he later named Alzheimer's disease. Depression and melancholia were already considered as separate. Kraepelin's first description of dementia praecox was published in 1896 in the 5th edition of his textbook, *"Psychiatrie"* (Kraepelin, 1896; translated in Cutting & Shepherd, 1987), refined three years later in the 6th edition. This is usually read in the eighth edition (Kraepelin, 1919) when he had included in the definition the "dementia simplex" described by Pick (1891) and by Diem (1903).

However, the term dementia praecox used in this way did not arise *de novo;* it was based on other descriptions of the 19th century. Pinel (1801) had used "demence" to describe psychotic states, and Morel (1852 & 1860) used the term "demence precoce" when he reported psychosis beginning in the teenage years. Snell (1865) had already separated primary paranoid states (primare Verrucktheit) from mania and melancholia, Kahlbaum (1874) had distinguished catatonia, and Hecker (1871) had described the phenomenology of hebephrenia, a description upon which Kraepelin drew later in his first, 1896 account. These authors tended to view these states as separate entities until Fink (1881) described mixed states of catatonia and hebephrenia. Kraepelin further described the phenomenology and clinical characteristics of dementia praecox but stressed the young age at onset and deteriorating course as the major distinguishing features of dementia praecox.

Twelve years after Kraepelin's first account, Eugene Bleuler questioned both these characteristics when he outlined his views of the prognosis of dementia praecox (Bleuler, 1908). He felt that the splitting or tearing apart of the psychic functions which occurred in the disorder was a more unifying characteristic than either age at onset or deteriorating course (although he acknowledged the view that the syndrome did usually deteriorate). Following

touching deference in his text to Kraepelin's contribution, he used the term "Schizophreniegruppe", the group of schizophrenias, to describe this. The first part of this term has stuck and is best described in a later account (Bleuler, 1911).

Bleuler stressed the phenomena of a disintegration of personality with disturbances of thinking, perception and sense of reality, and an incongruous affect. He considered that these were common to a group of heterogeneous psychotic conditions which could occur in clear consciousness without obvious brain disease. In the 1911 account, Bleuler also divided these phenomena into the primary or fundamental psychological dysfunctions of altered associations (disordered thought form and structure) altered affect, ambivalence and autism, and the secondary features such as delusions and hallucinations which he considered to be the result of the primary features.

Bleuler intended to narrow the concept of schizophrenia by emphasising these underlying or primary features; he considered delusions and hallucinations as non-specific. The opposite happened, possibly due to the *Zeitgeist* of psychoanalysis which was emerging (Murray, 1986). Bleuler's primary disturbances were difficult to define specifically and were seen widely by psychiatrists in their patients. Attention is drawn to them here because they infer the notion that several systems of the mind and brain are disturbed in schizophrenia, and that such disturbances may exist independently of the more dramatic phenomena which are stressed in descriptions of the clinical syndrome, e.g. hallucinations. Minkowski (1927) summarised the views of others (e.g. Stransky, 1904) and incorporated his own into a view of schizophrenia (he still called it dementia praecox) as a disorder of the harmonious interplay between several mental functions. This view is regaining popularity, particularly as explained by a mechanism of disordered neural connectivity. It underlies the approach taken here to examine the thesis in

terms of risk factors reflecting, and possibly affecting, several psychological and brain systems, both at the time of psychosis and before it begins.

The schizophrenia concept continued to develop over subsequent decades yielding rather than culminating in the current, operational, clinical definitions, although the concept is more fluid in many areas of research (discussed by Castle & Murray, 1992), concentrating on individual symptoms rather than the syndrome. Kurt Schneider steered definitions towards an exclusively phenomenological one when he published a list of symptoms which he considered to be of first rank importance (Schneider, 1959). With the addition of criteria for altered social functioning and chronicity, and exclusion criteria such as predominating depression and organic brain conditions, these form the basis of the modern operational definitions.

These modern classifications followed the demonstration in the early 1970's of unacceptable discrepancies in definitions of schizophrenia used by English and American psychiatrists (Cooper et al., 1972). This work precipitated the development and widespread use of operational diagnostic criteria, now available across the spectrum of psychiatric conditions. The trap of mistaking reliability for validity in these definitions is well recognised (Andreasen, 1995), but they have made much research evidence at least comparable between studies.

All operational systems rely on a largely cross-sectional definition of schizophrenia as a clinical syndrome, with the core features of certain types of auditory hallucinations, particularly voices heard talking in the third-person, changes in thought construction and form and, finally, bizarre delusions which often involve a person's ego boundary such that thoughts may be available to others or a person is influenced by outside forces (Table 1.1 a & b). These *positive,* psychotic phenomena comprising the core diagnostic features, usually occur together with changes in an individual's behaviour or social functioning. There may also be, so called,

negative features such as restriction of the range of emotions, and decreased ability to initiate thoughts and ideas. Some criteria, such as DSM, incorporate items regarding short-term course, something which may have a major impact on research into outcomes, and even on aetiological research where predisposing and precipitating factors may be confused with those which perpetuate the disorder, at least in the short-term (van Os, 1995).

None of the core features of schizophrenia is pathognomonic, although the presence of at least one, in the absence of an obvious organic precipitant such as drug misuse, is essential for the diagnosis. As Bleuler proposed, several psychological systems can be affected including perceptions in various modalities, the generation, construction and inferential use of thoughts, emotions and volition.

Andreasen (1995) has summarised the current views and their development. She emphasises the polythetic nature of schizophrenia and the division of its features into positive and negative, along the lines suggested originally by Jackson (1931) and later by Crow (1980). Andreasen notes that the array of signs and symptoms classified as positive or negative is often summarised according to the range of cognitive and emotional domains involved. Overall, schizophrenia must involve many brain systems or sub-systems (Table 1.2).

There are two competing explanations in anatomical terms. On the assumption that the functions and systems in Table 1.2 can each be localised to specific brain regions, the first suggests that schizophrenia may be a condition such as multiple sclerosis or cerebral lupus where multiple, discrete lesions in different sites produce a varied and heterogeneous condition (Carpenter et al., 1985; Andreasen, 1986). The second, again reminiscent of Bleuler, Stransky and Minkowsky, draws upon ideas of distributed parallel processing (Andreasen, 1986; David & Cutting, 1994). Abnormalities of the connectivity or "wiring" of the brain may produce

multiple effects depending upon the circuits involved and the site of the problem. The complexity of brain circuitry would ensure a multiplicity of inter-related symptoms (Mesulam et al., 1983; Braff, 1993) and other cognitive effects manifest only with specific tests.

Table 1.2 Relationship between features of schizophrenia and cognitive systems (Andreasen, 1995)

Schizophrenic symptom	**Cognitive system or subsystem**
Positive	
Hallucinations.....	Perception
Delusions.....	Inferential thinking
Disorganised speech / thought form.....	Language
Disorganised / bizarre / catatonic behaviour....	Behavioural monitoring
Negative	
Alogia.....	Conceptual fluency
Affective blunting.....	Emotional expression
Anhedonia.....	Experiencing pleasure
Avolition.....	Volition

Since the early 1970's this latter idea of disordered functional connectivity in schizophrenia has been amenable to direct investigation by functional neuroimaging techniques, first (Ingvar & Franzen, 1974) by crude, single photon emission tomography (SPET), and now by high resolution SPET, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Cognitive tasks, such as verbal fluency, are used to activate and suppress activity in specific cortical areas, and normal subjects are compared with those with

schizophrenia in terms of space and time (Liddle et al., 1994). As originally suggested by Wernike (1906), a disturbance of connections between the prefrontal and temporal cortices would fit many clinical data concerning schizophrenia. Recent ideas concerning causation might also fit in with such a model, including the timing of possible aetiological events in mid-pregnancy (Lewis, 1989; Murray et al., 1992; Jones, 1997) when relevant connections are being formed (Kostovic & Rakic, 1990).

McGuire & Frith (1996) noted that the direct evidence for *dys*connectivity in schizophrenia is as yet largely circumstantial, "its popularity owing as much to conceptual appeal as it does to scientific data". However, there is an opportunity to test, in biological terms, the model put forward by Bleuler. The notion of connectivity disturbance is mentioned as it is important for the arguments in this thesis. Several of the risk factors which are used to examine it may best be explained as operating within a neural environment where the establishment of connectivity is disturbed. These are the timing of developmental milestones, general intellectual ability and IQ, social behaviour in childhood, and the dimensions of the lateral and third cerebral ventricles. Those two structures are bounded by white matter including the corpus callosum, and by the diencephalon containing important relay nuclei, respectively.

This brief review has ignored many other attempts, particularly in continental Europe (see e.g. Hirsch & Shepherd, 1974), to identify and define the clinical borders of schizophrenia within mental illness. The review has stressed the widespread nature of the psychopathology in the clinical syndrome even when this is defined narrowly by modern criteria. The syndrome is a cross-sectional one but may be better thought of in longitudinal terms, with the clinical syndrome and its subsequent course as part of its evolution (Lewis, 1989). In terms of the brain and mind, what we call schizophrenia could alternatively be regarded as the *effects* of schizophrenia, not a disease in itself. If so, then the true definition of schizophrenia remains

almost as elusive as it has been over the rest of the century but at least we know where to look, in the structure and functioning of the brain.

Attempts at a dimensional categorisation, where schizophrenia represents the far end of a spectrum of abnormality, have not been considered here, despite the fact that a categorical classification of either the independent variable or the *dependent* variable (schizophrenia) could be argued to be anathema to this thesis. However, there has to be some certainty, or bearings on a map, when an idea is examined. The categorical concept of operationally defined schizophrenia is the more prevalent in the relevant literature and is used in this thesis. This approach is a necessary prelude to work on the disorder defined in a dimensional sense and which may ultimately be fruitless; the point is discussed again in Chapter 5. More of the descriptive epidemiology of the syndrome and evidence for its links with early life appear in Chapters 3 and 4. So much for cases, what about causes?

What is a cause?

According to the Oxford English Dictionary, a cause is that which produces an effect, the terms cause and effect being considered as correlative or reciprocal terms. Effect implies some active, or at least asymmetric relationship (Susser, 1991) between two or more factors, an idea which is discussed further below. However, a useful definition for medical use is that a cause is something which, when present, increases the frequency of a disease (Elwood, 1988) with the corollary that if you take it away, there is less disease. Rutter (1994) has summarised the basic experimental approach to establishing causation in a similarly simple way: "waggling" one variable to see if it causes another variable to move. I will now explore the development of these common sense views before turning back to schizophrenia.

What follows is influenced in particular by the writings of three individuals: Austin Bradford Hill, Mervyn Susser and Kenneth Rothman. The work of the psychiatrist turned philosopher, Karl Jaspers, is not discussed or quoted much but his contribution to ideas on causation must be acknowledged. His ideas continue to influence clinicians' thinking on causes of individuals' illnesses but appear to have developed in parallel to the work of the aforementioned. Read now, it is clear that Jaspers (e.g. Jaspers, 1946a) understood many of the problems with causation and explanatory theories with which I grapple below; the philosophical foundations were the same. However, Jaspers turned his discussions towards psychic life and explanatory psychology, away from general disease causation. His conclusions regarding explanation remain tangential to the specifics of this thesis and have not contributed greatly to the development of epidemiology as a method of identifying causes of disease.

The idea of causation and its investigation is fundamental to our understanding of and influence on the world. It is a concept which is learnt during early human development as examples of cause and effect are established, often by chance (Fraiberg, 1959). Notions of causes of diseases have evolved in parallel to understanding and models of the world and of the diseases themselves. A brief historical review is useful to establish how and why current views of disease causation have been established, and to illustrate some inconsistencies with respect to causation of schizophrenia which this thesis addresses. The conclusions can then be considered in a general epistemological context. The philosophical issues surrounding the nature of causality have been described as trecherous (Nicol-Smith, 1996). The great danger of over-simplification of these ideas is acknowledged. Given that a full account would have greatly extend the length of the thesis and changed its balance between theory and empiricism considerably, I have kept the account fairly short. I hope that justice has been done.

To set the scene, a "variable" or "factor" may be defined as any characteristic, attribute, phenomenon or event which can be measured and which can vary, be it from absent to present or in a more complex manner (Last, 1994). Variables may be found to be associated one with another either in day to day life or, more relevant here, in scientific studies. In epidemiological studies such associations may arise for a number of reasons of which cause and effect is only one.

The effects of chance variation on the sample(s) under study is something which many modern statistical methods are designed to define, most often by tests of the statistical significance, and by quantification of confidence limits around effects. Bias arises when the properties of the study itself, rather than the truth it attempts to capture, result in distortions in the findings. Confounding, on the other hand, arises when apparent associations between two variables are due to the independent effects of a third, giving rise to an alternative explanation for an association. These phenomena and the techniques for minimising them are all rehearsed in any textbook of statistics, epidemiology or research methods. Although their control accounts for a great deal of the effort in this thesis, they are not considered further here. It is the final explanation (cause) of associations between variables, cause and effect (which ever way around it be), that is discussed below.

Causation has interested philosophers for centuries, occupying a niche in epistemology, the debate over the verification of knowledge itself. The question is not only Susser's *"What is a cause and how do we know one?"* (Susser, 1991) but also the more fundamental, *"How do we know what we know?"* This question and the debate surrounding it has an ironic significance here given that the disordered formation of new knowledge, through a deranged process of inferential thinking, may lead to the delusional beliefs which form part of the schizophrenia syndrome (Table 1.2).

How is new knowledge accumulated? The philosophical explanation of "rationalism" predominated for centuries. Rationalists acquire scientific knowledge through reason and intuition, not through observations of the world, an approach which has become known as empiricism. Rationalism is, therefore, an inward-looking or closed philosophy. Mathematics would be the highest form of rational knowledge, built as it is, or was for centuries, upon an axiomatic framework by a process deductive logic; Euclid's geometry is a good example.

In the alternative doctrine of empiricism, judgements based upon natural phenomena are the ultimate source of knowledge. This doctrine has a long history but was developed and expanded following the Renaissance by Bacon, Locke and Hume. Bacon felt that "judgement" was the key to the logical processing of accumulated knowledge (Urbach, 1987). He likened rationalists to spiders, spinning webs from a finite source of knowledge whereas pure empiricists he likened to ants, collecting facts but finding no order in them. Bacon felt that the most effective empiricists were analogous to bees, collecting observations and processing them through the machinery of judgement and in so doing, producing a product of higher quality.

This form of knowledge based upon inductive inference or logic allowed prediction of future events, hence Bacon's view that "knowledge is power". Unfortunately, inductive inference may also be wrong; it is not self-contained and errors can creep in. Deductive logic on the other hand is pure but, being self-contained, cannot alone establish a theory of prediction. Inductive inference can never be certain because it is always possible that a crucial observation has not been made and assimilated into a model, an observation which might change the conclusion radically. Also, as Hume pointed out, inference does not carry the logical force of deduction (Hume, 1739); there is no "Q.E.D." to inductive logic (Beauchamp & Rosenberg, 1981; Rosenberg, 1993). Conclusive verification is impossible. This incompleteness to

inferential logic, particularly the danger of the missing observation or variable, is known as "Hume's problem".

Hume's problem remains a conundrum in this thesis; it is considered again in Chapter 5. Though sceptical concerning ultimate proof, Hume did propose some general rules to guide his own judgement regarding causality (see Part III, section IV of Hume, 1739). These included association in space and time, and specificity and gradients in associations. These are remarkably similar to rules considered below (see Table 1.3) which were put forward by epidemiologists two centuries later. As we shall see, the demand for a pragmatic framework to judge the increasing number of possible causes of medical conditions finally outweighed that for a satisfactory conclusion to the philosophical debate (Susser, 1986).

That debate continued after Hume, its protagonists unimpressed by his pragmatism which seems uncannily prescient, today. Attempts to provide a means of conclusive verification remained stagnant until Carnap proposed the "Logic of Probabilities" (Russell, 1912). Carnap abandoned the notion of absolute proof in favour of a relative system where the most probable solution, backed by the most evidence, was accepted. According to this logic, hypotheses became more or less probable depending upon the outcome of an experiment or observation, a view embodied in Heisenberg's "Uncertainty Principle". This influenced philosophy to abandon the search for causality in favour of a purely probabilistic view of the world. Thus, Reichenbach (1951) describes the scientist of the first half of the twentieth century as being more like a gambler than a prophet.

The inadequacies of probabilistic logic were exposed by Sir Karl Popper when he noted that statements of probability were neither deductions nor observations. In the context of a probability theory, they could be verified only by more and more statements of probability.

This "infinite regress" could not resolve Hume's problem. Popper (1965) turned on its head the impossibility of getting ultimate confirmation from observations. He proposed that knowledge accumulated only from falsification of prior explanations or hypotheses. Such hypotheses can never be proven by inductive logic. They can be only *dis*proved or falsified, when they can be discarded. Hypotheses that have been tested but not falsified are not proven but remain merely best descriptions of the truth until they are disproved by observation, hopefully to be replaced by others which better explain the empirical observations. Causality and determinism were quite acceptable to Popper (Buck, 1975) who rejected indeterminist logic and the uncertainty principle.

These Popperian views have predominated within scientific inquiry regarding causality, although jobbing scientists patently do not spend all their time falsifying hypotheses other than that of no difference, rather the reverse; it is difficult to do and journal editors are loath to publish such work. However, even if we have not learnt to think in terms of falsification, we have become accustomed to the use of hypotheses. The use and abuse of falsification in this thesis is discussed in Chapter 5.

Back in the theoretical camp some caution has been expressed regarding refutation based upon experiment and observation because these, too, may be subject to error (Brown, 1977). This problem affects the examination of the arguments presented in this thesis, just as it does all inquiry driven by hypotheses, null or otherwise. Also, predictions may arise from hypotheses that are not yet falsified but the predictions cannot logically be compared with observations which have failed to falsify the hypotheses - there is simply no logical framework for this. Finally, hypotheses depend upon a general theoretical framework, or "view of the world", which its itself subject to falsification. Once it becomes clear that the theoretical framework upon which hypotheses are predicated is incorrect, then knowledge advances by discarding that

framework rather than falsifying hypotheses which may or may not be compatible with it. Such is the nature of scientific revolutions (Kuhn, 1962).

How then have notions of *disease* causation evolved amongst these ideas? What is the problem with ideas concerning the aetiology of schizophrenia? Some of the first writings on disease causation are Hippocratic (Chadwick & Mann, 1950) where the relationships between disease and the physical environment of climate, water and earth were considered. The observations between, for example, illness and stagnant water were correct in some instances but the wrong causal inferences were drawn, an example of pure inferential logic and hypotheses based upon incorrect theoretical frameworks. Disease entities were not defined, resulting in the conflation of several illness such as malaria and dysentery, and the possible causal mechanisms were not understood or even conceived. In one sense the conclusions were valid; for instance, if individuals stayed away from stagnant water they were likely to remain more healthy than if they did not. In another sense they were mistaken; Hippocratic writers had not stopped to think that more than one process may be occurring, both in terms of there being a multiplicity of causes in the water, and many diseases or outcomes.

Concepts of biology and of disease did not progress far enough to allow a radical change in causal concepts until the 1800's and the discovery of the cell, although major advances such as the establishment by William Harvey of the circulation of the blood did occur before this. Observations on the environment and disease continued to be made, though, and the techniques of epidemiology began to be established. John Graunt's observations published in (1662) on the differential mortality and causes of death amongst different social groups, ages and sexes relied on the secondary analysis of routinely collected statistics - the Bills of Mortality from various London parishes. His conclusions relating poor social conditions to disease were valid but lacked any plausible mechanism and lay dormant for a century until they were discovered

by the "Sanitary Movement". John Chadwick in particular (Chadwick, 1842) pursued this line of inquiry and again made startling observations on social conditions and health. These observations were based on quite sophisticated analyses including "before and after" intervention studies. They resulted in effective preventative actions despite his erroneous causal explanations in terms of miasma ("bad air" due to decaying organic matter).

It was the discovery in the 19th century of "germs" and the development of the germ theory which presaged the concept of specific causes for diseases and the advent of an aetiological concept of disease. This was also a time when medical researchers using the beginnings of epidemiological methods began to adopt Bacon's concept of applying judgement to observations and so refining the products of inference. Pasteur takes much of the credit for the discoveries which underpin the germ theory and which influenced the process of judgement, but the development of a specific set of rules by which to infer causation of a specific disease by a specific micro-organism arose from the work of Joseph Henle and Robert Koch, teacher and pupil. The latter often gets the lion's share of the credit through the use of the term "Koch's postulates" to describe the criteria he presented in 1876 and 1890 with respect to anthrax (Koch, 1891). Henle published the general principals first, in 1840 (Rosen, 1937), and the term Henle-Koch postulates is used by some authors (Elwood, 1988; Last, 1995).

Koch's postulates for causation can be summarised as stating that:

the organism (cause) is always found with the disease

the organism (cause) is not found with any other disease

A third postulate, that:

the organism (cause) from one individual can cause the disease in another

was later dropped by Koch if the first two were satisfied.

Now there were rules to guide the reclassification of many diseases from descriptive clinical syndromes into aetiological entities; some such as pneumonia were split-up, others such as the many manifestations of TB were conflated. The neat, one-to-one relationship between cause and illness was a tremendous boost to medical research which still influences thinking today. However, as Susser (1991) points out, it also served to diminish awareness as to how *rare* such relationships are. It may also have held back the development of more complex causal models appropriate for other diseases which may have been dismissed because they did not fulfil the postulates. This point has been well put by Zuelzer (1967):

> *"Koch's brilliant achievements have made us unwilling to abandon his secure guideposts to causality, although, like the Newtonian Universe, they are valid only within a particular set of assumptions.....surprisingly, little is being said in our journals [of paediatric pathology and particularly of cancer] on the crisis of causality or the requirements for aetiologic hypotheses"*

Crisis is a strong word but the situation may be a warning for some aetiological research regarding schizophrenia. Other rules for judging causation, generally applicable to chronic, physical disease, may be more appropriate for schizophrenia, and may give fewer and more safe aetiological classifications. What are these rules?

Advances in the understanding of the causes of infectious diseases through the use of Koch's postulates and development of ideas and understanding of host immunity left chronic illness such as ischaemic heart disease, cancer, occupational diseases and major mental illness to be

explained. Single, necessary and sufficient causes (see below) for these conditions were found to be either very rare or non-existent.

In the 1940's and 1950's great strides were made in developing methods of studying the relationships between possible causes and these non-infectious diseases. The archetype was smoking and lung cancer, both of which had reached epidemic proportions. Case-control methodology and the calculation of odds ratios as a substitute for follow-up studies or randomised controlled trials, and the comparison of rates of illness in exposed and unexposed groups were all invented rather than discovered (Breslow, 1996). They were necessary for ideas of causation to develop further.

There was still no framework for establishing whether or not a factor such as smoking, ubiquitous as it was, could cause lung cancer; they were closely associated but the first two of Koch's postulates were never fulfilled; smoking was usually found without ill health and was also associated with other illnesses. The majority of heavy smokers did not get lung cancer and many people who did develop the disease were not the heaviest smokers. The corollary to the lack of a theoretical framework was the tide of disbelief in the possibility of a causal relationship that accompanied the failure of these postulates to be fulfilled.

With the increasing evidence of associations between a variety of factors and diseases it became clear that very few were specific, one-to-one relationships involving single causal factors and inevitable disease outcomes. A new set of standards was required in which to conceive and consider the empirical content of the causal hypotheses that were being developed. As described by Susser (1986), professional philosophers had not yet provided the framework to allow the "narrows and rapids of research" to be negotiated. The formalities of philosophy needed to be tempered by some "epidemiological sense". After attempts to adapt or

"water down" Koch's postulates (Yerushalmy & Palmer, 1959; Lilienfeld, 1959; Sartwell. 1960; see Dalen, 1969 for review) a new set of standards was proposed.

Table 1.3 Hill's criteria for judging causality

The strength of association	In relative terms, ideally rate ratios, the greater the effect, the stronger the association, the more likely it is to be causal. If a third factor is the true causal factor then its association with the disease must be even greater; the larger the effect, the less likely that is. Hill uses a similar argument for bias.
Consistency	If an effect is consistent across samples and research methods it is more likely to be causal than an effect found only in singular circumstances.
Specificity	An echo of Koch's first two postulates.
Time relationship	A cause has to predate an effect. Hill used this to argue that prospective data were more convincing than retrospective accounts.
A dose-response relationship	Evidence of a biological gradient in cause and effect made such a relationship more likely.
Plausibility	If a possible casual association is plausible then that adds to the evidence of causality.
Coherence	Similar to plausibility - if the evidence is along the same lines as other types of evidence, particularly non-epidemiological evidence.
Biological gradient	This was in reference to an experimental or intervention study where removal of a causal factor should decrease risk of disease. It is analogous to a dose-response relationship.
Analogy	If a similar factor causes a similar disease this lends weight to a causal argument.

Sir Austin Bradford Hill (Hill, 1965) suggested that several facets of an association needed to be considered when making the judgement as to whether it may be causal. These are

summarised above in Table 1.3. Hill was terribly humble about these criteria. He insisted that they were merely tools to aid judgement, not a means of suspending it and spuriously avoiding the problems of formal inferential thinking identified by Hume, Popper and other philosophers.

Hill's criteria have been enormously useful in providing a framework for inferential thinking about causation, and for considering evidence and observations as they arose. They have been applied in schizophrenia research by McGrath et al., (1995) with respect to a single categorical factor, exposure to prenatal influenza which failed to fulfil Koch's postulates, and cautiously by Lewis (1995) to the "secondary schizophrenias", states defined as occurring with coarse brain disease which may or may not cause the schizophrenia syndrome.

Susser (1973; 1976; 1991) arrived at a similar set of criteria. It is interesting to note that Hill's work is not referenced by Susser until 1991, and that Hill himself pays little attention to the work of the work of the Advisory Committee of the Surgeon General (US Dept. Health, 1964) which applied very similar criteria when judging whether or not smoking might cause lung cancer. Something of an argument arose in the literature as to whether the criteria were an English or American invention. Susser discusses and develops Hill's work in his exposition of causation published in 1991 where he stresses the importance of two features of an association. These were, "consistency" as revealed by its replicablity across time and researchers, and "survivability" over increasingly stringent research designs. Such designs can include a randomised controlled trial, the most stringent available, for only a very few putative causes.

I suspect the criteria were developed independently, as far as ideas ever are. Hill's account appears to develop from observation of several decades of research findings, inferring from the obvious to the obscure (Hill, 1965). Susser's account has a clearer philosophical pedegree, particluarly in later accounts (e.g. Susser, 1986), although being fair, Popper's views were

largely unknown at the time Hill was publishing (Buck, 1975). Regardless of their exact origins, Sackett et al., (1991) have shown how the criteria may be (and should be) applied in every day clinical practice, and Rothman (1976; 1988) has developed the arguments in terms of research regarding causation.

Rothman notes that causation is often a relative, not an absolute term. An example in psychiatry would be that regular consumption of ten units of alcohol each day for ten years may be said to *cause* alcohol dependence and liver cirrhosis. However, compared with the possibility of regular consumption of double this amount, such a course of action would decrease the likelihood of these conditions and may even be said to *prevent* them.

Table 1.4 Necessary and sufficient causes

	Necessary	*Sufficient*
A one-to-one relationship fulfilling Koch's postulates. Does not imply a sole or specific cause. Rare in psychiatry. Huntington's disease & its gene mutation? - see Chapter 5	+	+
A cause which is necessary but not sufficient; it is always present in disease but may be present without disease; e.g. a drug and a syndrome of dependence	+	-
A disease which may have several causes which each work in a one-to-one fashion.	-	+
Causes which are neither necessary or sufficient to cause disease. The majority of situations in psychiatry and the subject of this thesis.	-	-

Necessary and sufficient are terms which are often used with respect to models of causation (model being a term which has its own debates and various meanings; see e.g. Jaspers, 1946b; Susser, 1973) once a simple one-to-one relationship cannot apply. The meanings of the terms can be summarised by the matrix in Table 1.4.It is clear that in psychiatry the majority of associations exist within the final row where known causes are neither sufficient not necessary, and the logic of causal inference must be applied if judgements are to be made.

Rothman (1976) cuts through the endless debate over whether factors are necessary or sufficient like a breath of fresh air. Using as an analogy the question as to whether or not turning on a light switch causes a light bulb to glow, something which seems a reasonable causal inference, he notes that knowledge is rarely advanced enough to say that such a cause is sufficient; there are many necessary causes seen and unseen, known and unknown; the wire and the man at the generator having turned-up for work that day, etc., etc. It is futile to worry over whether individual causes are necessary and sufficient, although they may be more or less so.

Similar arguments pertain to disease aetiology. Here, a factor which seems to fulfil Koch's postulates may require numerous other circumstances to be in place in order for disease to occur. It is more valid to consider groups of causal factors together than to try to identify single causes. Many components of what Rothman calls a *causal constellation* will always remain unknown and it is misleading to assume that all individuals with a known part of that causal constellation have a similar increased likelihood of disease; they may differ in terms of the other, unknown parts of the causal constellation. In ignorance of these hidden causal components, the best that can be done is to assign an average likelihood to everyone exposed to a given causal factor or pattern of factors. Rothman concludes that, as knowledge expands, our estimates of the likelihood of an individual developing a disease will approach one of the extreme values of definitely yes or definitely no; risks of 100% or zero.

Within this common sense framework it is clear that the relative strength of an association, felt to be important by many in terms of aetiology (Hill, 1965; Sackett et al; 1991; Susser, 1992) depends as much on its prevalence as on its intrinsic, "aetiological force". Part of the constellation of a sufficient cause which is rare will appear to exert a strong effect in the unusual circumstances that it occurs together with other, more common, parts of that causal constellation. Furthermore, biological interaction between factors may be dependent upon the relative prevalence of others, and the acceptance of several, or many, possible sets of causal constellations means that there is no upper limit set on the proportion of disease which might be attributable to various individual causes. Induction periods cease to be a puzzle; it may take considerable time for composite sets making up a sufficient cause to fall into place and then for them to exert their biological effect, the total period being the induction time, and for disease to become manifest over a latent period (Rothman, 1981). Within this framework, predisposing, precipitating and perpetuating factors can be accommodated on equal terms although they can be useful in understanding the presence or absence of disease in individuals and are used a lot in psychiatry.

Reconsidering Hill's criteria, Rothman (1986) considers that only the criterion which is a *sine qua non* for causation is the temporal association between variables. Sackett et al., (1991) agree but argue that this is most useful only in a Popperian sense of falsification - if something occurs after the event it cannot have caused it; if it occurs before, it may or may not have caused it. However, Rothman emphasises that "Hill's criteria" are an aid to inferential judgement, nothing more. They are useful, nonetheless.

What are risks and risk factors?

Risk can be defined simply as a fraction: the number of ill individuals divided by the number of individuals that were at risk of becoming ill. It is, therefore, a term which properly applies to groups, not individuals, and over a specific time period. Such a risk may be used to assign to individuals a probability that an event will occur based upon the experiences of others.

In addition to this statistical meaning, lay usage includes an additional element. Here, the notion of the consequence of an event is important, as well as the chance of it occurring. This is not the way in which the term risk is used in this thesis.

Risk factor is a term which may also have a number of meanings. Broadly, a risk factor might be defined as any characteristic of either an individual or a group, be it genetic, environmental or life-style, which on the basis of epidemiological evidence, is associated with a health-related condition (Last, 1995). Factors associated with increased illness are usually referred to as risk factors to distinguish them from protective factors. This is merely semantics.

Somewhat more specifically and with some use of the notion of a cause, the term risk factor may be divided into:

Risk markers or indicators which are simply characteristics which are associated with increased probability of a disease or outcome but with no inference that there may be a causal link;

Risk modifiers or determinants, factors which are part of sufficient causes, either alone or with other factors;

Modifiable risk factors, a term intended to separate those risk determinants or modifiers which may themselves be modified and which are amenable to preventative action

The use of the term risk factor began with the Framingham study of the determinants of cardiovascular disease. Since the first publications from the study in the early 1960's its use has become so frequent that some use a disparaging term "risk factor-ology" to describe what they see as the poverty of some attempts to discover causes through the identification of ever increasing numbers of risk factors in their most general sense. As long as the goal is to identify modifiable risk factors then the approach seems reasonable. This thesis exists in the eye of that debate and may contribute something to it, at least in the niche of schizophrenia.

This brief discussion of what Susser (1973) has called "causal thinking" serves as an introduction to and justification for the thesis to be examined presented in the next chapter.

Chapter Summary

The thesis was introduced as being concerned with the causes of schizophrenia, as yet unknown. The thesis contains a debate as to whether some possible causes, or risks, may be adequately considered in terms of discrete entities, a general view of causation which has been prevalent in medicine, or whether they may be better considered as dimensional concepts.

The concept of schizophrenia was described and discussed. It was noted that schizophrenia is a diverse clinical syndrome, justifying the diverse risk factors which are used to examine the main argument set out in the previous paragraph. The operational criteria used to define schizophrenia in the two empirical sections of the thesis were introduced. It was acknowledged that these criteria may belie the richness of the clinical phenomena and their underlying mechanisms.

The notion of causation was introduced firstly in epistemological terms of establishing knowledge, then in historical terms of how associations, once established as real, are judged to be causal. The idea was discussed of one-to-one, necessary and specific causes so important in infectious disease and embodied in Koch's postulates. This was contrasted with a multifactorial model of risks, neither necessary nor specific but contributing to constellations of causes, some constituents of which may be unknown. These constituents may be considered as risk factors. Risk factors which both modify risk, rather than merely indicate it, and which are reversible should be the targets of aetiological research.

Chapter 2

Outline of the position taken in the thesis and the plan of its investigation

Position taken in this thesis

Adherence to thinking influenced by Koch's postulates may have resulted in the search for single, specific causes for schizophrenia. Rather than these specific, single causes, a dimensional view modelled on views of disease causation described in Chapter 1, with a dose-response relationship between cause and schizophrenia, may more accurately describe the true situation. Several different components of a causal constellation may be identified independently. Each may contribute not specifically to as many different outcomes as there are components, but to the causation of a single outcome.

The search for specific causes may, therefore, not only have been misguided, but also may have lead to the false inference that the majority of schizophrenia should be classified in terms of aetiological sub-types. Possible risk factors for schizophrenia that are in fact continuously distributed throughout the population, present to some extent in all individuals, are unjustifiably considered as binary, present or absent variables according to arbitrary criteria. When they are considered as present according to this strategy, they may have caused disorder or be manifestations of a single cause. When they are considered absent, they are excluded from having any effect.

The alternative situation for putative, continuous risk factors, which may be present to a greater or lesser extent in the majority or even all affected subjects, does not require sub-types based upon single causes. If the cause is not split, then perhaps the effect need not be split, either. A minority of unusual cases may be the exception. Acceptance of a dose-response relationship between risk factor and schizophrenia, and the notion of a variety of possible causal constellations, means that subjects with disease and varying doses of risk factor can all have the same condition, and that not all subjects with the risk factor need have the disease. In the spirit

of the thesis, this is not an all or none argument, merely a suggestion that there may be another way of looking at things.

Context

There are several causal explanations of schizophrenia current today, all summarised in any advanced textbook of psychiatry. These models of aetiology in schizophrenia have been summarised by Zubin and Spring (1977) when they first developed the notion of vulnerability. Details have changed over the past 20 years, particularly in genetics, but the general principles have not. The paradox of excluding from the schizophrenia syndrome those cases where there is likely to be a single causal factor operating in the brain has been noted in the Chapter 1. Lewis (1995), who applied Hill's criteria, has discussed the nosological status of these so called "secondary schizophrenias" and their relationship to the remaining bulk of the syndrome.

For this remaining majority of schizophrenia there are two general schools of thought. One supports causal heterogeneity and takes the view that schizophrenia will eventually be cleaved along aetiological lines into many different entities. The other states that a single cause, or class of causes, exists for the majority of the disorder, perhaps leaving a few more secondary cases to be identified. Proponents of these arguments are referred to colloquially as "splitters" and "lumpers", respectively.

The ingredients suggested for these different recipes are divided often into genetics, which seems the most likely explanation for many lumpers, and environmental factors, either psycho-social or physical, which are often posited for aetiological heterogeneity. Combinations are commonly suggested with different authors suggesting each might cause differing proportions of the disorder, or act in an interactive way. A stress-diathesis (or vulnerability) model (Zubin

& Spring, 1977) is an example of a model whereby combinations of factors might act. This thesis addresses only the individual factors (or ingredients) as a first step towards developing and testing further models involving many factors, something which is beyond the scope of this thesis.

Many individual environmental events are easily considered as categorical, all or nothing occurrences. For example, the experience of a stressful life event (Bebbington et al., 1993), pre-natal exposure to an infectious agent (O'Callaghan et al., 1989; McGrath & Murray, 1995) or head injury in childhood (Wilcox & Nasrallah, 1987) are all factors which have been posited as precipitating or predisposing factors in schizophrenia. Whether such apparently categorical events may exert a more continuous effect is considered in detail in Chapter 5. For example, the numbers of neural connections disrupted by a head injury may vary from none to many, despite the occurrence of the trauma having been a discrete, event. This argument recalls that of Rothman (1976) when he proposes causal constellations (Chapter 1).

Family history betraying genetic risk for schizophrenia, or other conditions, has been considered another categorical risk factor; people can be classified as either having an affected relative or not. This distinction has given rise to the familial-sporadic aetiological distinction proposed a decade ago by Murray and colleagues (Murray et al., 1985; Lewis et al., 1987). They suggested that genetics was a predominant cause of schizophrenia in those cases where the disorder was manifest in family members, whereas environmental factors would be important causes in the remaining, sporadic group. Moreover, families multiply affected with schizophrenia would provide a valuable resource for molecular genetic studies. This has proved to be the case (e.g. Polymeropoulos et al., 1994; Cloninger, 1994). However, susceptibility genes for this highly familial form of schizophrenia have yet to be identified with

certainty (Asherson et al., 1995; Harrison & Geddes, 1996). This precludes the investigation of whether they may also be relevant in apparently sporadic illness.

The proposals regarding the sporadic group have proved more controversial (Murray & Jones, 1996), although there are many environmental candidates. Particularly problematic has been the prediction that environmental factors affecting the brain would be of greatest importance in these sporadic cases and that, in consequence, structural brain abnormalities should prove to be more prevalent in the sporadic than in the familial form. This finding has not been consistent (reviewed in Murray & Jones, 1996), although there is some evidence that the predictions may hold for men but not women (Vita et al., 1995; Murray & Jones, 1996); another "splitting" argument.

Genetic risk itself has been reformulated as being a more dimensional concept. Defining such a categorical risk has always been problematic given the varying genetic distance between different classes of relatives (e.g. 1st and 2nd degree), the possibility of variable penetrance and the effects of genes at the molecular level (see Chapter 5). It has become clear that, in the majority of cases at least, there is no evidence of a single major gene or locus (McGue et al., 1985; Asherson et al., 1995). Multifactorial threshold models (Gottesman & Shields, 1967) and mixed genetic models (Morten & McClean, 1974) provide a better but still unsatisfactory fit to many available sets of family data (Asherson et al., 1995).

The family history variable itself has been redefined by Sham and colleagues to incorporate a dimensional content; positive and negative family history is weighted according to family (sample) size so to yield a continuous variable for genetic epidemiology (Verdoux et al., 1996). Such approaches can be applied to schizophrenia and to other disorders such as depression (Duggan, 1995). They have been found to provide superior explanatory models of both cause

and particularly course of illness because they can account for variable family size and age structure. Newer models involving quantitative trait loci as applied to other areas of behavioural genetics are discussed in Chapter 5.

Brain structure is mentioned here in relation to family history because it is used, in the guise of the dimensions of cerebral ventricles, as a test of the arguments in this thesis. The detailed background is in presented in Chapter 3.

Briefly, the finding by Johnstone and colleagues (Johnstone et al., 1976) of a higher mean lateral ventricle size in a group of subjects with schizophrenia compared with a group of controls suggested that some form of brain damage may contribute to the cause of schizophrenia. Size of these structures, like the size of the subjects themselves, is a continuous variable in the population. However, the findings were presented and received in terms of "enlargement", a categorical term implying that it was either present or absent. Subsequent studies working without a strict definition of enlargement, often using a statistical rather than a biological one, found it from time to time in a minority of cases. The conclusion was drawn that there was a sub-group of schizophrenia in which "enlargement" and brain damage occurred, but in the majority of the disorder it was absent. Applying the logic of Koch's postulates (Chapter 1), "enlargement" was associated with the cause of a minority of schizophrenia but had nothing to do with the cause of the rest which might, therefore, be an aetiologically distinct disorder.

Cerebral "enlargement" must be a little way down any causal chain (i.e. something must first cause *it* before *it* can cause schizophrenia) but it is used as the first test of the thesis that eschewing a single, one-to-one causal relationship and examining the whole distribution of the risk factor in the population and its association with schizophrenia will explain more and will

not require a subdivision of the disorder. As stated earlier, if the cause is not split, then perhaps the effect need not be split either. This is examined in Chapter 3 using data on cerebral ventricle dimensions from a cross-sectional survey of hospital admissions for psychosis and from non-psychiatric controls. Findings for schizophrenia are compared with those for affective disorder and controls.

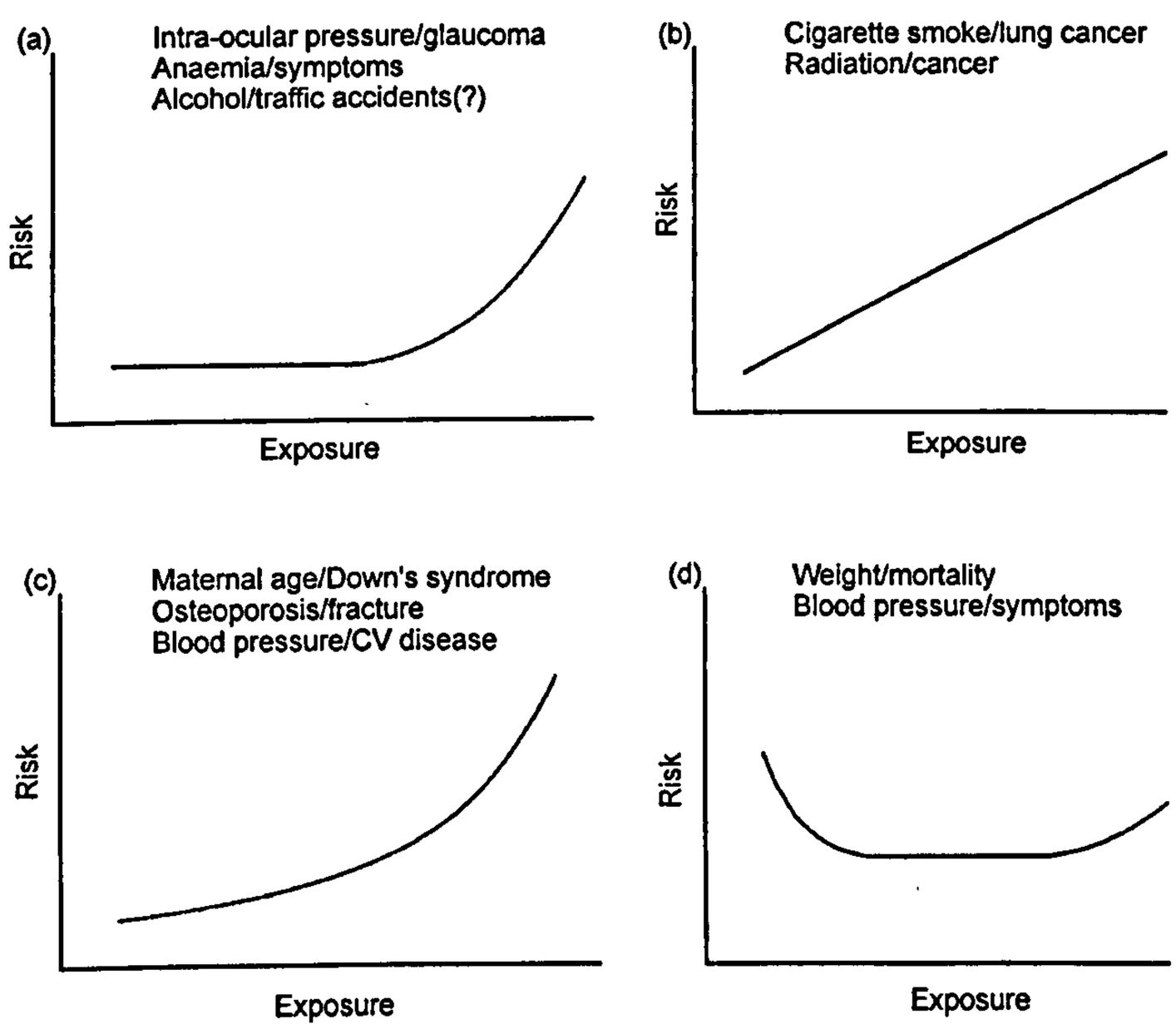
The second scene for examining the main arguments of the thesis involves the link between early developmental events and later schizophrenia. That such early events are relevant is suggested by associations between schizophrenia and winter birth, birth date at the time of influenza epidemics, minor physical anomalies, obstetric complications, behavioural differences and low IQ in children destined to develop schizophrenia, and from neuropathological findings best explained by perturbations in brain development. These associations are discussed in more detail in Chapter 4 and are reviewed elsewhere (e.g. Lewis, 1989; Murray, 1994).

The finding of such developmental riddles in the histories of around one third of individuals who develop schizophrenia (Rutter, 1984) has lead to the suggestion that they may suffer from a distinct, neurodevelopmental form of the illness (Weinberger, 1987; Murray & Lewis, 1987; Murray et al., 1988; Lewis 1989). As for cerebral ventricle enlargement, some of these risk factors are likely to be risk indicators, not modifiers (see Chapter 1). The thesis posits that their reclassification from continuous measures (e.g. IQ and perhaps some of the neuro-pathological findings) into binary, present or absent terms, and the application of the logic of Koch's postulates may underlie this classification of neurodevelopmental schizophrenia. Again, this may mask the possibility of a much more widespread association and effect between early life factors and later schizophrenia. This possibility is examined in Chapter 4 using developmental measures from a national birth cohort.

Examination of the argument

The investigation rests on identifying the nature of the association between a risk factor (e.g. cerebral ventricle dimensions or childhood IQ) and schizophrenia. For such continuous measures the possible relationships have been defined by Rose (1992). They are displayed in Figure 2.1 for a number of examples from physical medicine and public health; the figure is taken directly from Rose (1992). The terminology is also that of epidemiology and public health. For the purposes of this dissertation "exposure" could be better termed exposure to, or presence of a continuous risk factor such as IQ. "Risk" applies to a group phenomenon, as outlined in Chapter 1.

Figure 2.1 Four relationships between exposure to a causal factor and risk of disease



In Fig. 2.1a there is a threshold effect below which presence of the risk factor is not associated with disease (or increased risk of it). In this situation it might be considered valid to divide the

exposure at the inflexion point and consider it a binary, present or absent variable. In this situation, disease which arose in the presence of low levels of the factor (e.g. high IQ in schizophrenia) might rightly be considered as being aetiologically distinct. An example in psychiatry might be a life event increasing ambient stress above a threshold and precipitating illness. A similar argument might be made for the situation in Fig. 2.1d where one might also assume that the mechanisms of disease and the diseases themselves associated with very high and very low levels of the causal factor were different from each other. The inverse of the curve is familiar in psychology as the relationship between performance and anxiety described by Yerkes & Dodson (1908). In terms of disease, a psychiatric example might be the relationship between drugs and their states of intoxication or withdrawal.

The nub of the thesis is the comparison of the situation in Fig. 2.1a with those in Fig. 2.1b or Fig. 2.1c. The thesis states the latter may provide a better fit to some situations in schizophrenia and does not require the illness to be split in an aetiological classification; the risk factor applies to all disease in a dose-response way, something which Hill (1965) felt strengthened the case for involvement in causation. Application of Occam's razor, "the assumptions introduced to explain a thing must not be multiplied beyond necessity", suggests this situation should be expected in preference to heterogeneity. Of course, such relationships may hide other, more complex situations, particularly given the likely existence of Rothmans's causal constellations where the relative causal effect of a factor may depend on the prevalence of a number of others (see Chapter 1). Rose has pointed out (1992) that the situations in Figs. 2.1b and 2.1c are very difficult to tease apart empirically. It is difficult to define the exact equation for Fig. 2.1c due the requirements by relevant statistical models of enormous amounts of data. The samples used in Chapters 3 and 4 cannot do this with any precision. Merely, the line in Fig. 2.1b is contrasted with the situation in Fig. 2.1a so as to at least raise the possibility of alternative interpretations of the data.

Several steps are used in the analyses with some flexibility depending upon the circumstances of the particular variables. Associations between schizophrenia and continuous factors such as cerebral ventricle size are first defined with these variables classified as binary, using a variety of cut-off points such as one or two standard deviations above the mean. This allows replication of the usual approach in the relevant literature and raises the possibility of an association as depicted in Fig. 2.1a; the analysis is at a dead end with no possibility of finding evidence of any other form of relationship. The size of the effect is defined in terms of odds ratios. A more detailed, general rationale for using odds ratios is provided in the statistical analysis section of Chapter 3, in the context of some particular analyses.

Next, the possibility of a more general, linear, or dose-response relationship is explored simply by plotting the frequency distributions of cases and controls, and looking for overlap, anathema to adherents to Koch's postulates who may be happy with only the first step of analysis, and who might look for sub-groups of cases. The distributions can then be divided categorically into more than two levels and the association between each section of the distribution and risk of schizophrenia defined, again in terms of odds. If there is evidence that the risk increases from baseline (e.g. the lowest category of risk factor) in steps throughout the distribution, then an association as depicted in Figs. 2.1b or 2.1c is a possibility, and the factor can be modelled legitimately as a continuous variable. *The thesis rests upon the general hypothesis that this evidence will be found.* The situation in Fig 2.1d can be eliminated in this scheme.

Finally, it is informative to consider strength of association not only in terms of relative odds (i.e. size) once the *shape* of that association has defined, but also in terms of the amount of variation in the risk of schizophrenia that can be explained by a factor under study. Figure 2.2

is adapted from Susser (1973) in order to illustrate the concept of *proportion of variance explained.*

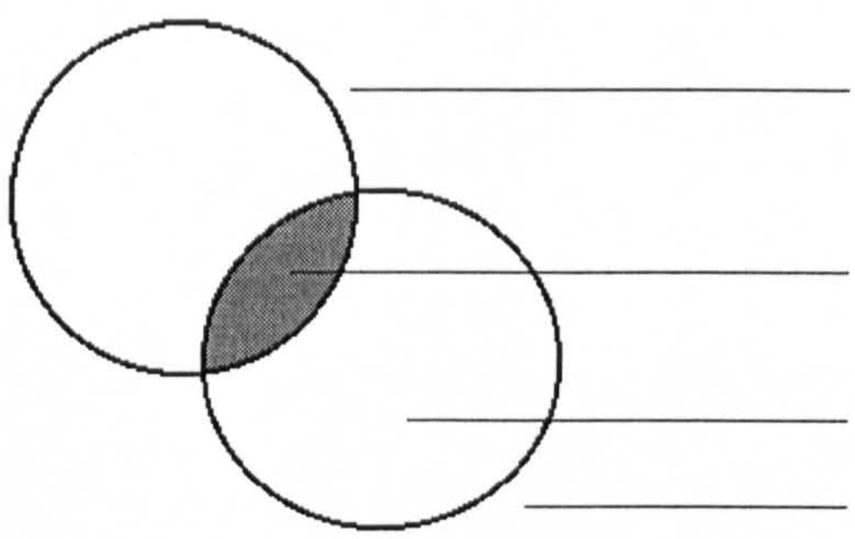


Figure 2.2 Proportion of variance explained.

The Venn diagram illustrates the association between such variables, each circle representing one variable with the area of each representing the amount of variation within that variable. Variance describes that variation in quantitative terms being a measure of dispersion of the values in a sample. The association between the two variables is represented by the overlap. The stronger the association, the stronger the correlation (r) and the larger the proportion of variance (r^2) in the dependent variable (e.g. risk of disease) accounted for by the independent variable or risk factor. A specific, one-to-one cause would account for a proportion of explained variance approaching 100%, and the circles in the figure would overlap. This concept is explored again with examples in Chapters 3 and 4, together with further consideration of the detailed statistical analyses appropriate in particular situations.

An alternative approach using positive predictive value (PPV), or proportion of subjects correctly predicted in logistic regression models is not presented; exploratory analyses for the material in Chapter 4 indicated that this proportion was zero, a result due largely to small numbers and lack of statistical power. However, it is most unlikely that the true PPV is zero; the positive, albeit small proportions of variance explained derived from standard regressions better illustrate the point relevant to the thesis.

Statistical power is not considered in detail in each of the empirical sections. There are many hypotheses which are tested in order to investigate the main arguments of the thesis. Each of these attempts either to exclude the null-hypothesis or to define the precision (confidence limit) of an effect such as an odds ratio has different statistical power. It would be tedious to define them all, particularly when the examination in the thesis is an opportunistic exercise using existing data. These were the most suitable data-sets I could find but they are not perfect.

Moreover, the thesis is not primarily concerned with the effects themselves but with a consideration of the merits of two approaches to analysis. For the primary hypotheses in each section which replicate other work, statistical power is adequate at greater than 70% for 95% confidence. For example, a three-fold increase in the occurrence of values in the largest third of cerebral ventricle size with 121 cases and 67 controls (see Chapter 3) gives 92% power, a two-and-a-half fold increase could be detected with 83% power. The important point is that the methods proposed as being more informative than these simple analyses, that is the investigation of *trends* in associations, always have higher statistical power because more of the variance, or information within the data is used in the calculations (Armitage & Berry, 1987). Some broad considerations of statistical power arise from time to time in the thesis but specific power calculations do not.

Chapter Summary

This chapter served as a link between the general consideration of schizophrenia and of causes contained in Chapter 1, and the main empirical sections in Chapters 3 & 4. The individual risk factors examined in these sections were introduced in the context of the debate over causation in schizophrenia. It was noted that these are continuous factors in the population and do not naturally assume values which are either normal or abnormal, present or absent. The assumption that this is the case is prevalent in the literature and may act as a constraint on causal research. Splitting continuous values into a binary classification means that the factor is, *de facto,* excluded from having any causal role over the range of values defined as normal or absent.

Four models (Figure 2.1) of possible relationships between continuous risk factors and disease were presented. The main hypothesis was declared: the situations in Figures 2.1 b and c, where there is no evidence of a threshold effect, will fit the data examined in the ensuing chapters better, or more completely, than the situation in Figure 2.1a. Parsimony alone predicted that the risk factors need not be split into discrete categories. Furthermore, if the risk factors were not divided but allowed to have a defined role throughout their range, then a binary, aetiological classification of the disease itself would be un-necessary. This is the situation in many chronic physical diseases where the notion of necessary and specific causes suggested by Koch's postulates has already been relinquished. It was pointed out that with the available data the hypothesis can and will be examined only in terms of individual factors, not several factors acting together, but the logic of the argument should not change in a multivariate situation.

The general statistical approach taken in the thesis was outlined.

Chapter 3

Cerebral ventricle dimensions as risk factors for schizophrenia and their specificity with respect to affective psychosis.

An epidemiological approach to a 20 year old puzzle.

Introduction

This chapter describes a study aimed at defining the relationship between the size of cerebral ventricles and schizophrenia. The main argument of this thesis predicted that there would be a general, dose-response relationship between ventricle size and risk of the disorder in the majority of affected individuals and, conversely, that the notion of a sub-group of schizophrenia due to some form of categorical "enlargement" is a less than adequate explanation of the data.

The existence of structural brain changes in schizophrenia is widely accepted, particularly that of large lateral cerebral ventricles. This story began in the first quarter of the century with neuropathological studies and *in vivo* studies using pneumo-encephalography (See Falkai & Bogerts, 1995 for review; and also, Huber, 1964). After a period of decades when psychological and psychodynamic aetiologies (rather than mechanisms) held sway, interest was rekindled by a seminal study by Johnstone and colleagues who used the relatively new technique of computerised X-ray tomography (CT) of the brain. Johnstone and her colleagues reported significantly larger lateral cerebral ventricle area in a group of 13 individuals chronically hospitalised for schizophrenia compared with eight normal volunteers (Johnstone et al., 1976). The results are summarised in Figure 3.1, a facsimile of the figure in their original Lancet paper. This report spawned many others, the majority of them replicating the finding (Lewis, 1990). Along with other evidence, such as the efficacy of antipsychotic drugs and the role of genetics in aetiology, the results shaped the view of many contemporary researchers who would acknowledge that the phenomenological features of the schizophrenia syndrome are related to in some way to deviations in brain structure and function (Murray, 1994), even if its causes and precipitation are multifactorial.

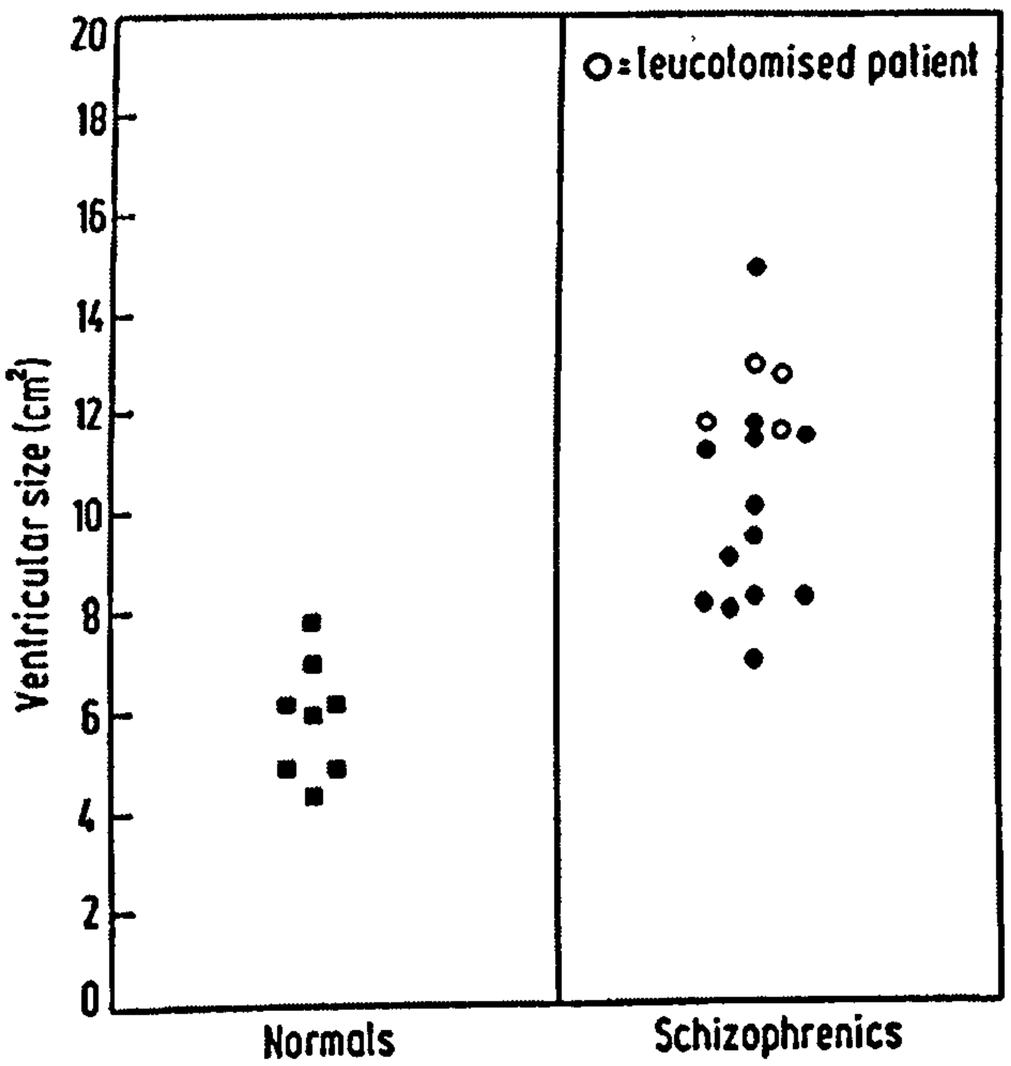


Figure 3.1 Facsimile of figure from Johnstone et al., (1976). VBR in normal subjects and subjects with schizophrenia.

Some people remain sceptical (Chua & McKenna, 1995) and some major questions remain unanswered. Reviews of the literature (Lewis, 1990, van Horn & McManus, 1992) have highlighted the curious trend in more recent X-ray computerised tomography (CT) studies to report increasingly small differences between controls and groups of cases with schizophrenia. This secular trend is almost certainly due to the use of more representative samples of both cases and controls. Nevertheless, these authors and other reviewers (Raz & Raz, 1990) did confirm that significant differences in the size of the lateral cerebral ventricles exist between cases of schizophrenia and controls, albeit small. Small differences in the brain are likely to be of practical as well as statistical significance.

The second problem, central to this thesis, concerns the definition of just what constitutes pathology. This has been a problem for all neuroimaging research, particularly when the size of structures which vary continuously in the general population has been the focus of attention; the distributions of structural dimensions in comparison groups have consistently shown

considerable overlap (Smith & Iacono, 1986; Smith et al., 1988; Harvey et al., 1990b). The main question posed in this Chapter is whether the relationship between cerebral ventricle size and risk of schizophrenia is best described by the situation in Figure 2.1a, where there would be risk only after a threshold of "enlargement" is crossed, or by the situation in Figure 2.1b (or 2.1c) where there is a more general, dose-response relationship.

As ventricle size is so dependent upon head size, researchers have often divided values of the former by the latter to give a quotient measure, the ventricle : brain ratio (VBR). Smith & Iacono (1986) gathered all studies published up to 1985 and plotted the mean VBR for cases and controls, dividing the 14 studies which showed an association between larger ventricles and schizophrenia and the 7 that had not. Figure 3.2 reproduces their results. The tendency is clear for the study result to be dependent upon the control samples rather than the schizophrenia samples; it was a definition of "normal" vs. "abnormal" which varied between studies, not the data for cases of schizophrenia. As in all epidemiology, the sampling of controls is as vital as the case definition.

Several explanations of the variation in control sample values have been put forward. Some authors (Raz et al., 1988; Smith et al., 1988) have drawn attention to bias that may arise from using medically screened, "supra-normal" subjects as controls, rather than healthy community volunteers; even the latter may be biased towards a high prevalence of psychiatric disorder (Halbreich et al., 1989; Shtasel et al., 1991). Confounding by characteristics such as age, sex and social class has been paid attention only in varying degrees. There are documented ethnic, gender and socio-economic status differences in head size (Khang-Cheng et al., 1980; Andreasen et al., 1990a) that merit further examination in normal people and in patient series. These are rarely reported (Harvey et al., 1990a).

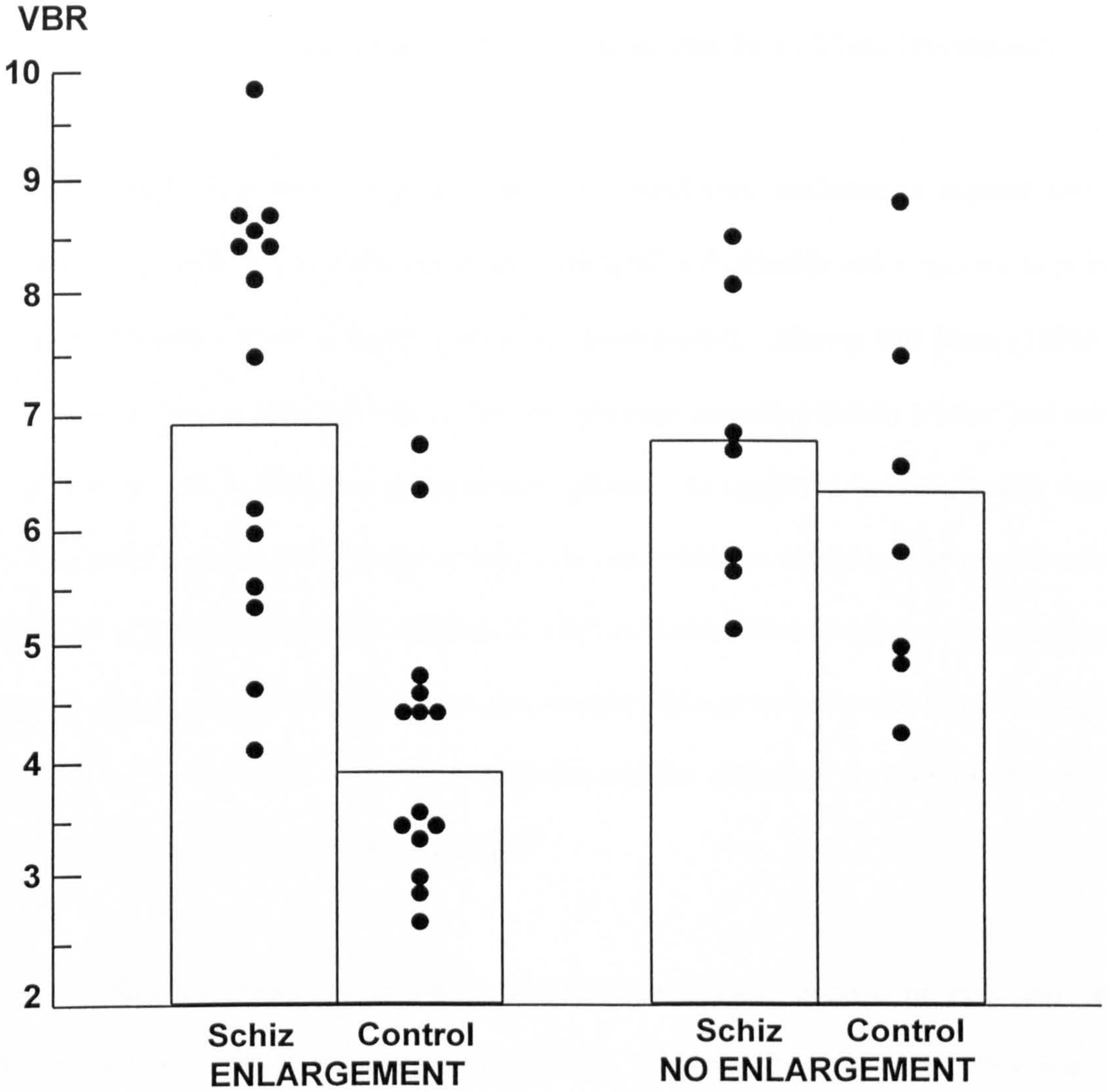


Figure 3.2 Smith & Iacono's (1986) demonstration that variation between studies demonstrating "enlargement" of VBR depended upon control samples, not cases.

Clinical heterogeneity of the case groups is another possibility which has been examined. This line of reasoning assumes that the proportions of clinical sub-types varies between study samples and that the true effect for a particular sub-type is always diluted, sometimes such that no effect is distinguishable in a particular study. Good versus bad outcome, poor premorbid functioning, prevalent negative symptoms, early age at onset, chronicity of symptoms and

presence of tardive dyskinesia, cognitive impairment and putative causal factors such as obstetric complications and family history of schizophrenia, have all been investigated.

Lewis reviewed this literature as of 1990. He found little evidence to suggest that such heterogeneity might be an explanation, although tardive dyskinesia and cognitive impairment were consistently related to larger ventricles. More recently, Murray and Jones (1996) were prompted by Vita et al., (1994) to review the literature regarding family history and cerebral ventricle size, and to undertake an empirical analysis. As suggested by Vita, gender appeared to be a modifying factor with larger ventricles in men without a family history of schizophrenia compared with men with such a history or with women in either category. Data on controls would be required to confirm the interaction but the findings underline the level of complexity which is likely to underlie the true explanation and the difficulty, particularly in terms of a large enough sample size, of investigating it.

The problems of variability of effects and the considerable overlap of case and control distributions emerged in the literature rather later than they might have, possibly due to the startling original findings of Johnstone et al., (1976) shown in Figure 3.1. Their data were consistent with the majority of cases having larger VBR than controls, and thus with the notion of enlargement having a 1:1 relationship to schizophrenia, something behaving as an all-or-nothing event and fulfilling one of Koch's postulates for causation (see Chapter 1). Such an elegantly simple situation in such a complex disease as schizophrenia would be hard to give-up.

But what is "enlargement"? As stated above, subsequent studies soon showed that this 1:1 relationship was by no means always the case (see Smith & Iacono's work, above & Figure 3.2), highlighting the question as to how "enlargement" should be defined. Weinberger and colleagues (1979) demonstrated that only 40% of a group of 58 subjects with chronic disease

had VBR outside the control range, with only 10 having "enlargement" agreed by radiologists' opinion. In keeping with the time trend noted by van Horn & MacManus (1992), Andreasen and her colleagues (Andreasen et al., 1990) showed that less than a third (29%) of 108 subjects with DSM-III schizophrenia had VBR values outside (larger) than 1 standard deviation (s.d.) from the control mean (n=75), with only 6% outside the 2 s.d. range - not much more than the figure expected by chance which could not be excluded as the explanation. These findings were confined to men. Both sexes with schizophrenia had similar values of VBR but the values for female *controls* were surprisingly large given expected population norms (Zatz & Jernigan, 1983). This is a further demonstration that the choice of controls is just as vital as the choice of cases (choice being an unfortunate though common term as random sampling is necessary before any statistical tests become valid).

This overlap of case and control values being the rule, and with the lack of a conceptual causal model which could incorporate it, there has been debate over whether ventricle size could really have anything to do with schizophrenia, despite the statistical association in terms of mean values first demonstrated in 1976 by Johnstone and colleagues (Birley, 1992); this is the 20 year old puzzle in the title of this chapter. Certainly, the majority of CT studies and more recent work using Magnetic Resonance Imaging (MRI) stick to this difference in mean values as their effect of interest, usually adjusted for confounding, rather than attempting a more complete explanation. The phenomenon of overlapping distributions remains largely unexplained even though the image techniques and their spatial resolution have moved on.

It is curious that the debate has gone quiet given that the researchers have remained largely the same individuals. Just as for the early CT studies, statistical power and representative samples remain a problem in MRI work. Chua & McKenna (1995) have reviewed 26 recent structural MRI studies of schizophrenia published since 1986, the time when the issue of control

distributions was being debated in the CT literature. My calculations from their data indicate that there was an average of only 29 cases (s.d. 11.7, max. 54) and 26 controls (s.d. 12.5, max. 60) per study.

For teasing-out the meaning of the overlap in distributions of values between cases and controls, CT retains the advantage in terms of the feasibility of scanning large, representative samples. This is the case even though there may still be selection bias, and *relatively* small samples with type II errors, particularly where the true effect sizes are small. Few CT studies have included more than 100 patients with schizophrenia together with controls (Takahashi et al., 1981; Gross et al., 1982; Owens et al., 1985; Sacchetti et al., 1992; Andreasen et al., 1990a). The study reported here is an attempt to address some of these problems and test the ideas set out in Chapter 2.

This case-control study was designed to explore the relationship between the functional psychoses and intra- and extra-cerebral cerebrospinal fluid (CSF) spaces using high resolution CT imaging. This study has a sample size sufficient to assess both schizophrenic and affective psychoses, with adjustment for confounding by sociodemographic characteristics. To avoid the unsolved problem as to how to define abnormality (Smith & Iacono, 1986), and specifically what constitutes ventricular enlargement, the distribution of ventricular size in the controls was used as the basic unit of measurement. Affected cases could then be examined in terms of where they lay within this distribution, the relative positions of cases and controls being expressed as an odds ratio, which could be equated with risk, allowing the direct estimation of both effect sizes and the contribution of sampling error. The results could be compared directly across studies, and contrasted with multiple regression or analysis of variance, the techniques which have generally been employed in this area (Zatz et al., 1982; Zatz & Jernigan, 1983; Pfefferbaum et al., 1988; Harvey et al., 1990a; Jernigan et al., 1990) and replicated here.

Volume and area measures of the lateral ventricle (LV) are said to correlate well (Penn et al., 1978; Zatz & Jernigan, 1983; Reveley, 1985), hence the frequent use of VBR. However, some have suggested that volumetric measures might give better discrimination between cases and healthy controls (Gado et al., 1982; Raz et al., 1987). By using a unifying scale (the population distribution), this analytical approach allows the degree of similarity between results based on areas and volumes to be quantified. Simple ratio measures of ventricle and cranium size were not used because of the evidence that the relationship between the two is not a simple, linear one (Harvey et al., 1990a); statistical regression techniques are preferable.

The study is predicated on there being an association between schizophrenia and both ventricle volume and extra-cerebral CSF. The intention was to quantify the size of the association, in order to be able to evaluate its aetiological or mechanistic rôle, and to establish whether ventricle size should be considered a continuous risk factor for schizophrenia, or whether increased risk of the disorder is confined to a subgroup of individuals with particularly large ventricles. These possibilities are modelled by Figures 2.1a and 2.1b (or c), respectively. The main hypothesis was that the former model was more likely given the considerable overlap in ventricular dimensions found in previous studies of schizophrenia and comparison groups. If the association were to be specific to schizophrenia with respect to affective psychosis the evidence for a possible aetiological or mechanistic role of ventricle size in the former condition might be strengthened.

The opportunity was also taken to examine the association between brain structure and possible aetiological factors, namely, obstetric complications and family history of psychosis, hypothesising that each would be associated with large ventricles in schizophrenia.

Finally, an attempt was made to replicate associations in schizophrenia between large ventricle size and both young age at onset and abnormal premorbid social adjustment, and to examine the effect of chronicity in order to explore the notion of clinical heterogeneity in the association between sizes of cerebral ventricles and schizophrenia sub-types.

Method

Selection of cases and controls

Cases

Cases of functional psychosis were drawn from two cross-sectional samples of consecutive hospital admissions to three South London hospitals serving two adjacent health districts; The Bethlem Royal Hospital, the Maudsley Hospital and Dulwich North Hospital serving South Southwark and East Lambeth, respectively. The first is the Camberwell Collaborative Psychosis Study (CCPS; Jones et al., 1993a) which the author managed for one year. This involved all three hospitals. The second sample was drawn only from Dulwich North Hospital (Harvey et al., 1990a) and is referred to here as the North Dulwich sample.

Sampling procedures were very similar for both studies except that in the CCPS there were two sampling periods, March 1987 - February 1988 and October 1988 to August 1989. In the former period, consecutive admissions were drawn only from the Bethlem and Maudsley Hospitals. In the latter period consecutive admissions from one of the three hospitals were excluded every third month in rotation in order to limit the number of eligible patients to an amount manageable to one interviewer, the author. Also, re-admissions in the CCPS were recruited only if they had a mother or father available for interview. This was due to the study having an emphasis on premorbid history and, again, limited manpower resources. The implications of this are reviewed in the discussion section of this chapter. The North Dulwich sample was recruited during 1986/7 and involved all consecutive admissions as the sampling frame.

The identification of potential cases of psychosis was the same for both surveys. Each weekday morning all relevant hospital wards were contacted and all admissions aged 16 to 60

years were screened on the basis of information from medical staff or from the patients themselves. They were recruited if delusions, hallucinations, catatonia (although there was none) or formal thought disorder, as defined in the Research Diagnostic Criteria (RDC) of Spitzer et al., (1978), were present without evidence of focal neurological disease, or other organic cause such as epilepsy, RDC drug use disorder or alcoholism. Over the entire period of both surveys 5 individuals were involved with this screening. The inter-rater reliability between pairs of individuals using this screen was shown to be good, the lowest un-weighted kappa value being 0.87 ($p<0.001$).

For those who were screened positive for psychosis and, in the CCPS, had a parent available for interview, initial diagnostic assessment comprised the Present State Examination (Wing et al., 1974) and case note review. Cases were included in this study if, in addition to their psychotic symptoms, they fulfilled the RDC for schizophrenia, schizo-affective disorder, bipolar I disorder, manic disorder or major depression and, having given informed consent, underwent CT scanning. All RDC diagnoses for subjects in this CT study were made on the basis of review of PSE interviews and case notes by two investigators, one the author. Disagreement occurred in only three cases out of 216 cases and a consensus diagnosis was made after discussion.

In view of statistical power constraints and the literature review, particularly that concerning structural neuro-imaging in affective disorders (Scott et al., 1983; Dolan et al., 1985; Schlegel & Kretzschmar, 1987; Johnstone et al., 1989; Swayze et al., 1990; Andreasen et al., 1990c; Coffey et al., 1993), an *a priori* decision was made to combine the RDC categories of major depression and bipolar disorder into a single "affective disorder" category. There was no *a priori* decision taken regarding the status of schizo-affective disorder and schizophrenia other

than to combine them only if effect sizes and patterns of effects appeared similar in the two groups.

Controls

Controls were unpaid volunteers actively recruited from three main sources: a Salvation Army training college in Camberwell, South London, Camberwell Job Centre and the employees of the Institute of Psychiatry and associated hospitals. Inclusion criteria for volunteers were the same as for the patients, other than that controls were excluded if there was evidence, from a semi-structured interview, of the RDC disorders mentioned above, including alcoholism. The interview has been published by Lewis (1993).

This analysis concerns CT scans from the complete admissions and control series; technical CT analyses concerning a sub-group of 37 of the schizophrenia cases from the North Dulwich sample and from different controls have been reported elsewhere (Harvey et al., 1990 a&b), as have data from the CCPS concerning premorbid behaviour (Foerster et al., 1991 a&b), socio-economic status (Jones et al., 1993a), life events and follow-up (Bebbington et al., 1993; van Os, 1994).

Socio-Demographic and Clinical Assessments

Socio-economic status at birth or during early childhood was assessed for both cases and controls using the Registrar General's classification of paternal occupation (see Jones et al., 1993a). This was re-coded into three groups; social class 1 and 2, class 3, or class 4 and 5. Ethnicity was classified on the basis of appearance and place of birth of parents as either white European or other ethnic group. An estimation of verbal intelligence was derived from the New Adult Reading Test (Nelson & O'Connell, 1978; Nelson, 1982) except in 74 cases from

the North Dulwich sample where the verbal sub-set of the WAIS (Wechsler, 1955, 1958 &, 1975) was employed to yield a comparable measure (Crawford et al., 1992).

In the cases but not controls, raters (not the author) blind to proband characteristics including diagnosis, each interviewed mothers concerning family history (as defined by the Family History RDC, Andreasen et al., 1977), premorbid personality and obstetric history. Obstetric complications (OC's) were rated as absent or definitely present according to the scale of Lewis et al., (1989), except that rapid labour was no longer classified as an OC; this scale has been validated by O'Callaghan et al., (1990). Details of these assessments are published elsewhere (Foerster et al., 1991 a & b). Age at onset was defined as the age at which the proband first saw any medical practitioner for psychotic symptoms, and pre-morbid social function was rated according to the scale of Phillips (1953).

CT Scanning

Axial CT scans were performed on one Siemens 9800 scanner between 1987 and 1992, a period during which repeated scanning of a phantom indicated that there was no long-term drift in attenuation values. Pilot, lateral skull X-ray ensured standard initial orientation in the transverse plane. Slices 1 cm thick, parallel to the floor of the anterior fossa and ascending to the vertex were analysed at an independent viewing console (IVC). Three raters, blind to other information on the subject, each rated similar proportions of both case and control scans; inter-rater reliability was high ($r>0.96$ for each measure).

Intracranial area was measured on each slice by summing all pixels in the range 0 to 100 Hounsfield units (HU; Hounsfield, 1973) within the skull. A border just peripheral to the brain/cerebrospinal fluid (CSF) boundary of the third and lateral ventricles was traced manually

and the IVC required to sum pixels from 0 to 25 HU within this area. Areas of the lateral and third ventricles were measured in all slices where they appeared, and a LV volume constructed by adding together all the area measurements of its body, occipital horns, and frontal and anterior horns (Penn et al., 1978). Third ventricle volumes were also calculated, with particular care taken to differentiate the inferior segment of the third ventricle from the inter-peduncular fossa. However, the superior and inferior limits of the third ventricle can be difficult to see clearly in some subjects so that, given its regular and slit-like shape, a single cross-sectional area taken from a slice through the middle of the ventricle might be regarded as the more valid measure. An estimate of intracranial volume was made by adding together the intracranial areas of four slices; the most superior slice on which the anterior horns alone were visible (v.s.), the slice below this and the two slices above. These slices, yielding a truncated intracranial volume henceforth referred to as simply "intracranial volume", were chosen as the majority of the ventricle slices lay within them, and the relevant data were available on all subjects. The maximum areas of the lateral and third ventricles, and the corresponding intracranial area for that slice, were identified for each subject.

Sulcal area was measured, using the most superior slice that still contained lateral ventricular fluid, by tracing manually within the skull and cerebrum an annulus that contained the entire cortical outline and sulcal spaces. The IVC summed all pixels between 0 and 25 HU inside this trace to give an estimated area of sulcal fluid. The boundaries of the inter-hemispheric fissure (IHF) were traced on the same slice and measured similarly. Right and left sylvian fissures were defined manually, taking the most superior slice where the anterior horns were visible without the occipital horns or body of the LV coming into view. The areas were measured as for the IHF. Global visual ratings of the cortical sulcal spaces (0-3), the inter-hemispheric fissure (0-2) and the sylvian fissures (0-3) were also made using reference photographs for each

rating. This methodology has been used in several studies and is also described elsewhere (Owen et al., 1988; Harvey et al., 1990b; Jones et al., 1993b; Lewis, 1993).

Statistical Analysis

The general strategy was as outlined in Chapter 2. Data were first described graphically and using routine summary statistics. Associations between socio-demographic variables and ventricle size were defined in the controls alone so as to judge possible confounding, defined as an independent association between a third factor and exposure (ventricle size) in the controls, between the disease and that third factor. The latter associations being judged from the literature.

The prevalence of ventricle dimensions in case groups outside either one or two standard deviations from the control mean was calculated. This was not part of the strategy for examining the thesis but allowed for comparisons between this study and earlier works.

The next analyses, involving expression of associations as odds ratios, and logistic regression models of the binary, case or control outcome, are unusual in the structural brain imaging literature, despite being appropriate methods for case-control studies (Breslow & Day, 1980). Sandercock (1989) has provided a general introduction to this approach with respect to the neurosciences, and the applicability of the techniques to psychiatry has been reviewed elsewhere (Lewis and Pelosi, 1990; Tsuang et al., 1993). The approach to quantifying continuous risk factors is novel in this area and forms an important aspect of the thesis.

The distributions of areas and volumes in the control group were divided into thirds (tertiles). If there were no differences between cases and normal controls, a third of the cases, too, would

have been found within each of these tertiles, and, with the lowest tertile as base line, the odds ratios equal to one.

Two specific hypotheses were tested. First, that cases would be more common in the largest third of the distribution compared with the remainder of possible values. Second, and more importantly, that there would be a linear trend for cases to be found more frequently in higher tertiles. Adjustment was made in these analyses for confounding factors using classical epidemiological statistics, such as those of Mantel and Haenszel (1959), and logistic regression analysis (Breslow & Day, 1980). Where analysis involved cases only, analysis of variance (ANOVA) was used. Analyses involved both area and volumetric measures so as to examine their relationship.

The percentage of variance in sizes of the lateral and third ventricles explained by being either a case or control (i.e. that attributable to diagnosis/disease process), following adjustment for confounding factors, was defined using linear regression. Ventricle size (lateral ventricle volume and third ventricle area separately) was the dependent variable and intracranial volume as the first independent term, followed by entry of sex, social class and ethnic group together, and finally case versus control. This was done for schizophrenia, schizophrenia plus schizoaffective disorder and then for affective psychosis. The change in r^2, the percentage of variance explained, was calculated for each step together with the statistical significance of that change, the primary interest being the final step of addition of diagnosis.

Justification of statistical approach employing odds ratio analysis to define trends in the association between psychotic diagnoses and continuous risk factors

The underlying assumption to the study was that there is a causal association, possibly indirect, between structural brain changes, betrayed as enlarged CSF spaces, and psychosis. The most appropriate quantitative measures of any 'causal effect' are ratio measures of association comparing affected and unaffected subjects, such as rate ratios, risk ratios or odds ratios. Thus, one can use information such as 'cases of schizophrenia are twice as likely to have large ventricles than are normal controls' (i.e. an odds ratio of 2, or odds of 2 to 1) to make a judgement on this assumption, just as a betting man would use the odds of a horse winning in order to judge where to place his money. Odds ratios (OR) can be tested statistically against the null hypothesis that the true OR is one (no association), significance being two tailed as the sample value could be either higher or lower. A 95% confidence limit for the true OR may be calculated, giving an indication of the effect of sampling error which can be compared with other studies.

The most powerful study design to investigate this assumption would be a prospective study of the psychiatric outcome of a random sample of subjects in whom brain structure had been previously defined. The rate of development of, say, schizophrenia could be calculated in subjects with large ventricles and compared to the rate in subjects with small ones; the ratio of these two rates would give an estimate of the 'aetiological force' of large ventricles. Such a study is impractical on a large scale with outcomes as rare as the psychoses; many thousands of subjects would be required.

Case-control methodology enables the reciprocal study to be undertaken; the frequency of occurrence of large ventricles, or any other exposure of interest, is calculated in cases and controls, and the ratio calculated. When this is done in terms of odds, and the disease is rare

(<5%), the resulting odds ratio gives an estimate of the more preferable measure, the rate ratio that would have been obtained in a prospective study (an algebraic fluke). Thus, in the above example, an odds ratio of 2 from a case-control study would allow us to infer that, if the ideal, prospective study were undertaken, subjects with large ventricles would develop schizophrenia at approximately double the rate of those with small ones.

This strategy of analysis can be extended so as to avoid the problems of having to define "enlargement" of structures, and the conceptual difficulty that arises when one talks of differences in the *group* means when individual values show considerable overlap between groups. The distribution of values in the control sample, assumed to represent the population from which the cases were drawn, can be taken as the basic unit of measurement and divided into equal parts, in terms of numbers of controls falling into each. The probability, or odds, of the affected cases falling into each of these categories can be calculated and expressed as a ratio with the controls, the null hypothesis being that this ratio will be unity; cases will be distributed similarly to controls. If there is a linear trend in incremental change of the odds ratio across the distribution, this is evidence that a simple linear model best fits the data. Here, all one would be concluding is that, say, large ventricles are more likely to occur in schizophrenia, and by inference, that the larger the ventricles, the more likely is schizophrenia to develop. The case-control design puts the association the other way around: if you took two people exactly comparable other than that one had schizophrenia, that person would be more likely to have larger ventricles than the former. This is similar to the notion that the more cigarettes a person smokes, the more likely they are to develop lung cancer, or, if two people were comparable other than the fact that one had lung cancer, that person would be likely to smoke more cigarettes than the former. There is no inference that the healthy person is a non-smoker, or that the schizophrenic subject has enlarged ventricles whilst his colleague's are of normal size.

There are technical reasons why this risk is usefully expressed as odds. The scale of effect is a unitary one which allows comparison between exposures and across studies, and facilitates judgement of causality. Thus, a calculated odds ratio for the season of birth effect based on a 10% winter birth excess in schizophrenia (Bradbury & Miller, 1985) is approximately 1.1, whereas that associated with presumed genetic, familial associations (Gottesman & Shields, 1982) is nearer 10, similar to that seen in smoking and lung cancer, and indicating a stronger, and probably more direct causal association in the latter case. It should be noted that these conclusions from ratio measures do not equate with the importance of the proposed aetiological factor in terms of control of disease prevalence. This depends on how common both disease and exposure are in the population.

Thus, the advantages of odds ratio and confidence limit analysis include the direct estimation of an effect size and a separate estimation of the effect of sampling error, ready comparison of results within and between studies, and the exploration of specific dose-response relationships. Some of these advantages over comparisons between mean values and analysis of contingency tables using chi squared statistics have been well reviewed by Sandercock (1989), Lewis & Pelosi (1990) and Tsuang et al., (1993).

Results

Description of samples

Of 317 eligible patients, 216 agreed to take part in this CT study. The majority (141, 65.3%) were from the CCPS sample, and 75 (34.7%) from the North Dulwich sample. All cases were urban; 161 (74.5%) were from the local catchment area in South Southwark and East Lambeth, the rest residing in adjacent areas (15, 6.9%) or other London postal districts areas (40, 18.5%). There were sixty-seven controls.

The socio-demographic details of the case groups and controls are displayed in the top section of Table 3.1. The controls were of higher childhood socio-economic status than the cases, particularly those with schizophrenia, and contained more white European subjects although, in this age group, the proportion of such subjects in the controls was similar to that found in the local district. Cases and controls were scanned at similar ages but within the case groups, those with schizo-affective disorder had a later age at onset and more chronic course in terms of weeks as an in-patient. Controls had considerably higher verbal IQ than the cases (118 vs. 103, 95% confidence interval (c.i.) difference 12.7 - 17.7, p=0.001). Men with schizophrenia had an earlier mean age at onset than did women (21.2 yrs vs. 25.2 yrs, 95% c.i. difference 0.7 - 7.0 yrs, p=0.02), whereas the ages at onset for men and women with schizo-affective and affective disorder were almost identical.

Table 3.1 overleaf.

Table 3.1 Sociodemographic and clinical characteristics of the sample, and mean volumes for cases and controls (cm^3). RDC diagnostic categories.

		CONTROLS	SCHIZOPHRENIA	SCHIZOAFFECTIVE	AFFECTIVE*
NUMBER		67	121	41	54
MALE : FEMALE (% MALE)		43:24 (64%)	91:30 (75%)	21:20 (51%)	19:35 (35%)
CHILDHOOD SOCIO-ECONOMIC STATUS**	I - II	49	29	12	21
	III	12	44	15	14
	IV - V	6	47	13	15
ETHNICITY WHITE EUROPEAN		61	64	20	18
OTHER		6	57	21	36
AGE AT CT SCAN (S.D.)		31.7 (6.9)	28.9 (8.1)	35.1 (9.4)	32.9 (8.8)
VERBAL I.Q.*** (S.D.)		118 (6.6)	101 (13.2)	105 (12.6)	106 (14.0)
AGE AT ONSET **** (S.D.)		-	22.7 (7.2)	25.1 (8.1)	23.3 (7.5)
WEEKS AS IN-PATIENT (S.D.)		-	29 (79)	49 (75)	26 (37)
INTRACRANIAL VOL. (CM^3)		655.8 s.d. 50.0	637.7 s.d. 47.2	619.0 s.d. 54.6	624.9 s.d. 57.4
LATERAL VENTRICLE VOL.		12.4 s.d. 8.1	13.8 s.d. 9.3	16.0 s.d. 10.7	12.7 s.d. 9.7
THIRD VENTRICLE VOL.		0.91 s.d. 0.52	1.03 s.d. 0.57	1.03 s.d. 0.63	0.95 s.d. 0.6
MAX. THIRD VENT. AREA		0.53 s.d. 0.28	0.62 s.d. 0.32	0.62 s.d. 0.35	0.58 s.d. 0.33

Unadjusted Intracranial volumes differ (F=4.4, p=0.002). Ventricle volumes similar.

* 38 Mania/bipolar, 16 major depression.
** Recoded from Registrar General's classification - see text.
*** From N.A.R.T. or verbal subset of W.A.I.S. - see text.
**** Age when first saw a psychiatrist.

Table 3.2 Ventricle volumes and sociodemographic features of the controls (n=67)

		Intracranial Volume	Total Lateral Ventricle Volume	Third Ventricle Volume
All Controls (95% c.i.)		655.8 (643.8 - 667.8)	12.4 (9.3 - 15.72)	0.91 (0.78 - 1.03)
Sex	Men	683.3	13.9	1.07
	Women	606.7	9.7	0.61
	95% c.i. diff.	59.6 - 93.5 p<0.001	1.2 - 8.2 p=0.04	0.23 - 0.7 p<0.001
Ethnicity	White European	658.4	12.2	0.9
	Other	629.5	13.9	0.87
	95% c.i. diff.	-12.7 - 70.6 p=0.2	-0.54 - 8.6 p=0.6	-0.4 - 0.48 p=0.8
Childhood Social Class	I - II	664.8	14.4	0.94
	III	631.2	10.8	0.82
	IV - V	631.8	12.4	0.84
	F ratio	3.1 p=0.05	1.1 p=0.3	0.28 p=0.8
Association with Age at Scan		r = -0.03	r = 0.1	r = -0.03
Association with Verbal IQ		r = 0.3 p=0.04	r = 0.2 p=0.15	r = 0.3 p=0.02

CT scan measures in the controls.

Table 3.2 shows the intracranial and ventricular volumes for the controls. Men had larger intracranial and ventricle volumes, a reflection of their generally larger body size. There were trends (not significant) for white Europeans to have larger intracranial volumes but smaller ventricles. Those in higher socio-economic groups during childhood tended to have both larger cranial vaults and ventricles. The same patterns were observed for area measures. Thus, any differences in CT scan dimensions between cases and controls may have arisen either from the socio-demographic differences between them, or from true associations with the diseases under study; adjustment for these factors was necessary.

Correlations between age at CT scan and both ventricular and intracranial volumes were small (Table 3.2), and none was significantly different from zero. Intracranial volume was strongly associated with ventricle volume; correlations ranged from 0.25 to 0.44 for these measures, and all were statistically significant ($p<0.01$).

There were modest but statistically significant correlations between verbal IQ and both intracranial and third ventricle volume. Correlations between IQ and lateral ventricle measures were smaller and not significant. These associations between IQ and both cranial and third ventricle dimensions were confounded by sex and social class; all controls spoke English as their first language. Men and those in higher social classes had larger heads (Table 3.2) and also scored better in the IQ assessments. Mean verbal IQ for men was 120, and for women, 116 (95% c.i. diff 0.5 - 7.5, $p=0.03$). There was a gradient of IQ scores down from the higher socio-economic groups to the lowest. Using ANOVA, both sex and social class remained as significant independent effects on IQ (sex $F=7.02$, $p=0.002$; class $F=4.02$, $p=0.05$; no interactions).

Ventricle dimensions in cases and controls.

Figure 3.3 is a scatter plot of lateral ventricle volume in cases and controls. A very similar plot was obtained for third ventricle area (Figure 3.4). The considerable overlap between cases and controls is obvious whereas any evidence of a group of cases with large dimensions is not. The eye is drawn to one or two cases with large dimensions but it should be remembered that these very rare values would be expected to occur by chance more commonly in the larger case group than in the smaller control group. The plan of analysis including dividing the distributions into categories (thirds) will negate these subjects having any undue influence on the results,

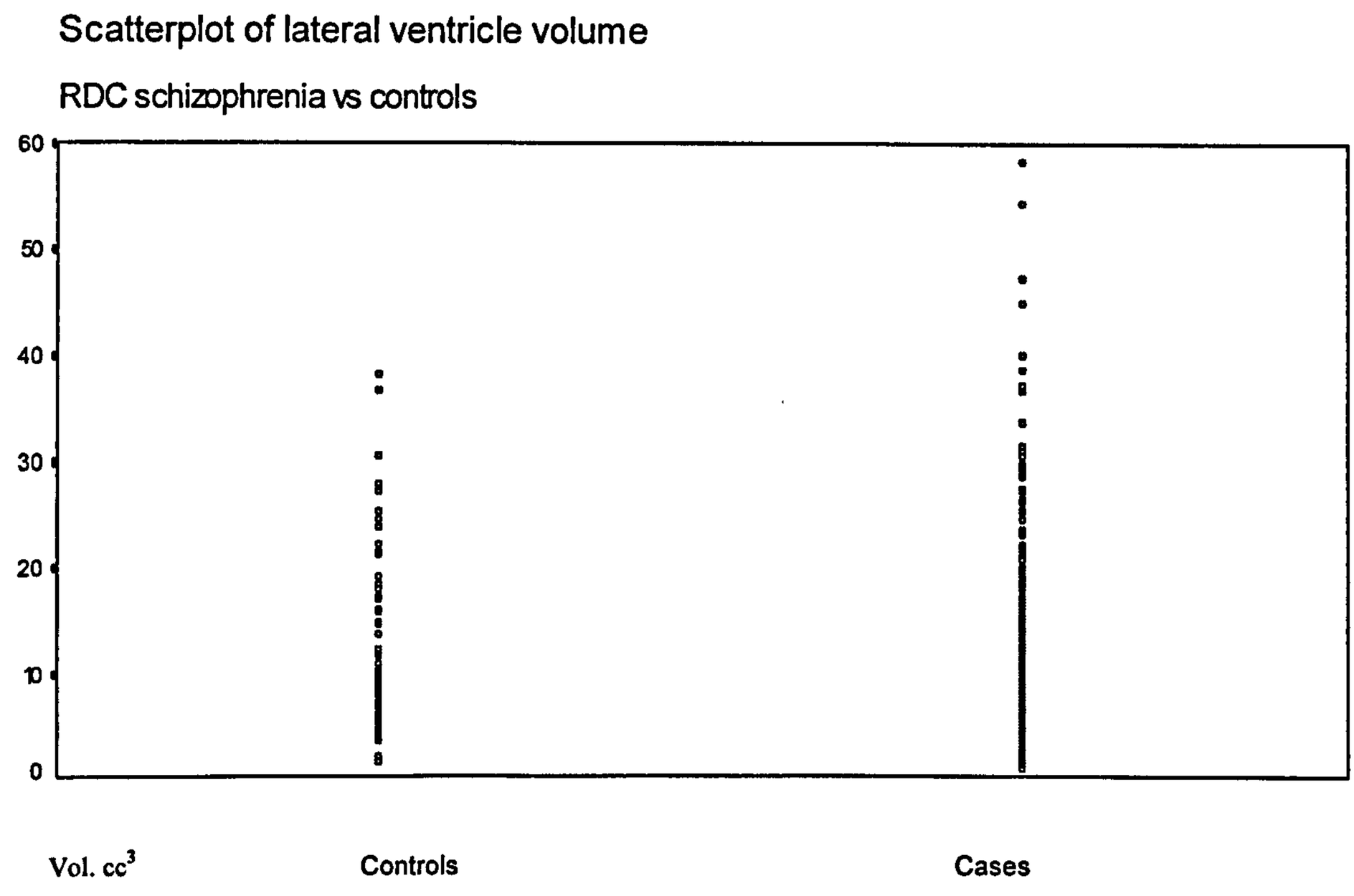


Figure 3.3 Lateral ventricle volume. Schizophrenia cases and controls

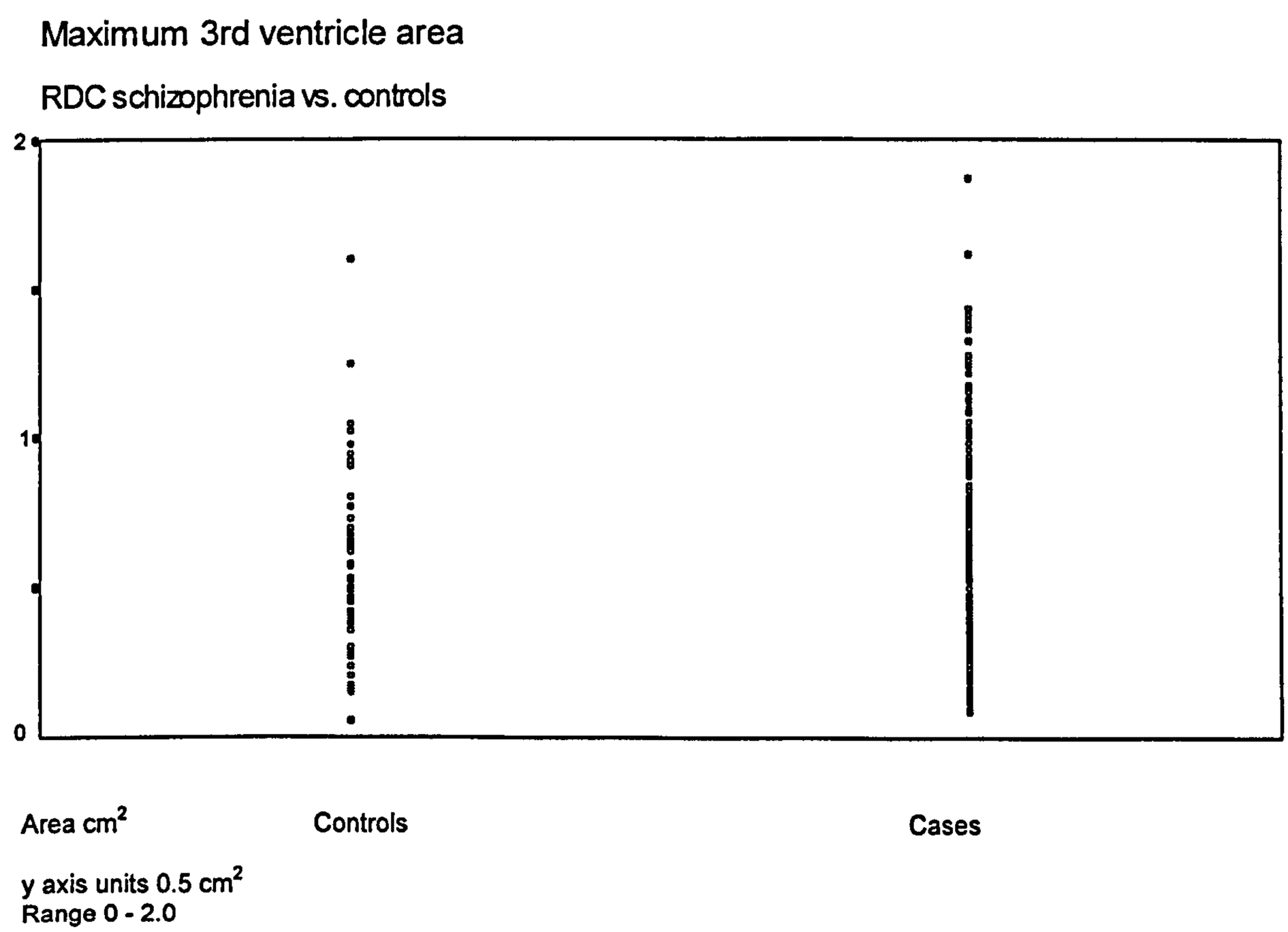


Figure 3.4 Third ventricle area. Schizophrenia cases and controls

in contrast to the case if analysis relied solely upon comparisons between mean values. This crude graphical representation does not account for possible confounding factors such as differences between sociodemographic variables in cases and controls.

Table 3.1 (page 86; bottom section) shows the mean LV volume for all cases and controls. The distributions of all the area and volume measurements showed a slight positive skew. Figures 3.3 and 3.4 show the situation for lateral ventricle and third ventricle volumes, respectively. Log-transformation made very little difference and un-transformed data were used throughout all the analyses for clarity and uniformity. Standard deviations were similar between groups. There was a consistent pattern for controls to have significantly larger intracranial volumes than all the case groups ($p<0.05$ for all contrasts), whereas their ventricles were smaller, i.e. larger craniums containing brains with smaller ventricles. However, analysis of the controls alone demonstrated that these findings could have been the result of the differing socio-demographic and ethnic characteristics of cases and controls. Also, the strong correlations between intracranial volume and ventricle size demonstrated in the controls meant that the combination of smaller heads and larger ventricles found in the cases was unexpected, and that intracranial volume, too, must be taken into account when investigating dimensions of the ventricles. A very similar pattern of results was seen with area measurements.

Schizophrenia cases versus controls

Table 3.3 shows the prevalence of case values greater than one and two standard deviations from the control mean for lateral ventricle volume and maximum third ventricle area. For simplicity, only percentages are shown. Un-transformed data were used just as in the rest of the analysis, results from log-transformed data being very similar. The results indicated that extreme values were more common in the case groups, unadjusted for confounding, particularly

for the third ventricle (e.g. for third ventricle area greater than 2 s.d. above the control mean there were 9.9% schizophrenia subjects versus 3.0% of controls; top two cells on right hand side of Table 3.3). However, this approach emphasises that if these statistical definitions of "enlargement" had any biological value then over 90% of each case group does not have "enlargement", and so is unaccounted for in terms of any mechanistic or causal model which might be constructed on the basis of these data.

Table 3.3 Prevalence of values for lateral and third ventricle sizes greater than one and two standard deviations above the control mean.

	Lateral ventricle volume greater than		*Max. third ventricle area greater than:*	
	1 s.d.	*2 s.d.*	*1 s.d.*	*2 s.d.*
Controls (67)	16.4%	4.5%	11.9%	3.0%
Schizophrenia (121)	19.0%	5.0%	23.1%	9.9%
Schizo-affective (41)	29.3%	9.8%	24.4%	9.8%
Affective (54)	24.1%	7.4%	24.1%	9.3%

This analysis of a categorical definition of "enlargement" can be taken a little further by adjusting for confounding factors such as sex. The thesis states that such more sophisticated categorical definitions will still yield only inadequate explanations of the data. So as not to show any undue allegiance to any single categorical definition, and to lead into the next stage of analysis where the thesis is examined more directly with relative measures of effect, "enlargement" was defined in an alternative way as values greater than the 75th centile of control values and odds ratios of prevalence of "enlargement" calculated. Tables 3.4 to 3.6 show the results of such analysis for schizophrenia, schizo-affective disorder, both of these categories combined, and affective psychosis, both adjusted and unadjusted for confounders. The results illustrate several points.

Taking Table 3.4 for schizophrenia, almost a third of the cases had enlargement compared with a quarter, by definition, for the controls leading to crude odds ratios (OR) of around 1.4. Adjustment for confounding lead to an increase in these effects in all factors except intracranial volume. For maximum third ventricle area the effect was quite substantial (adjusted OR 3.9; 1.6, 9.5) suggesting that this may be an important variable with respect to schizophrenia, and yet the analysis tends to hide the fact that a quarter of unaffected subjects (controls) were exposed to this influence. The contrary is found for third ventricle volume which is really measuring the same structure. The explanation may lie in the arbitrary nature of the cut-off for "enlargement" - another definition would have yielded more comparable results - or a more technical problem regarding the shape of the third ventricle which may differ between cases and controls.

The results for schizo-affective disorder are shown in Table 3.5. Here the effect of adjustment for intracranial volume and for confounding by sociodemographic factors made an even more striking difference to the effects for ventricle measures. Adjustment for sociodemographic factors indicated that any differences in intracranial volume - head size - between cases and controls were accounted for by these factors, there being no effect for diagnosis (bottom right hand cell in Table 3.5). Similar effects were noted for this definition in affective psychosis (Table 3.6) although none reached statistical significance.

The implication for the thesis is that any analyses of "enlargement", however defined, must be difficult to interpret without this form of adjustment. Even so, different definitions lead to quite variable results and the fact that disease in a large proportion of the cases, and health in a large proportion of controls, remains unexplained in terms of ventricle dimensions indicated that such definitions were indeed inadequate in this sample.

Table 3.4 Association between RDC schizophrenia (n=121) and abnormal cerebral dimensions: categorical approach.

	Percentage (N) cases with enlargement*	Raw OR (95% c.i.)	Adjusted OR** (95% c.i.)
Lateral ventricle volume	29.8 (36)	1.3; 0.6, 2.5; p=0.5	2.6; 1.0, 6.3; p=0.04
Maximum third ventricle area	41.3 (50)	1.4; 1.0, 2.1; p=0.06	3.9; 1.6, 9.5; p=0.003
Third ventricle volume	32.2 (39)	1.4; 0.7, 2.8; p=0.3	1.6; 0.7, 3.9; p=0.3
Intracranial volume***	29.8 (36)	1.4; 0.7, 2.7; p=0.4	1.2; 0.4, 3.8; p=0.7

1 case excluded due to missing social class data. OR = Odds Ratio

* Enlargement defined as larger than 75th percentile of control values n=67). Effect for intracranial volume calculated for *small* volumes below 25th centile for controls.

** Odds ratio adjusted for intracranial volume, sex, childhood social class, age at scan and ethnic group.

*** Volumes *below* 25th percentile. Odds ratio adjusted for sex, childhood social class and ethnic group.

Table 3.5 Association between RDC schizoaffective disorder (n=41) and abnormal cerebral dimensions: categorical approach.

	Percentage (No.) cases with enlargement*	Raw OR (95% c.i.)	Adjusted OR** (95% c.i.)
Lateral ventricle volume	39.0 (16)	2.0; 0.8, 4.5; p=0.1	6.0; 1.6, 22.7; p=0.01
Maximum third ventricle area	36.6 (15)	1.6; 0.7, 3.8; p=0.3	5.3; 1.5, 19.6; p=0.01
Third ventricle volume	31.7 (13)	1.4; 0.6, 3.3; p=0.4	3.7; 1.1, 12.2; p=0.04
Intracranial volume***	46.3 (19)	2.6; 1.1, 6.0; p=0.03	1.1; 0.3, 4.4; p=0.9

1 case with missing social class data excluded

* Enlargement defined as larger than 75th percentile of control values (n=67). Effect for intracranial volume calculated for *small* volumes below 25th centile for controls.

** Odds ratio adjusted for intracranial volume, sex, childhood social class, age at scan and ethnic group.

*** Volumes *below* 25th percentile. Odds ratio adjusted for sex, childhood social class and ethnic group.

Table 3.6 Association between RDC affective disorders and abnormal cerebral dimensions: categorical approach.

	Percentage (No.) cases with enlargement*	Raw OR (95% c.i.)	Adjusted OR** (95% c.i.)
Lateral ventricle volume	35.2 (19)	1.4; 0.6, 3.1; p=0.4	2.1; 0.8, 5.5; p=0.1
Maximum third ventricle area	35.2 (19)	1.4; 0.6, 3.1; 0.4	2.6; 0.9, 7.4, 0.07
Third ventricle volume	33.3 (18)	1.5; 0.7, 3.4; p=0.3	2.1; 0.8, 5.4; p=0.1
Intracranial volume***	51.9 (28)	3.6; 1.6, 7.6; p=0.002	1.4; 0.4, 4.5; p=0.6

* Enlargement defined as larger than 75th percentile of control values. Effect for intracranial volume calculated for *small* volumes below 25th percentile of control values - see text.

** Odds ratio adjusted for intracranial volume, sex, childhood social class, age at scan and ethnic group.

*** Volumes *below* 25th percentile. Odds ratio adjusted for sex, childhood social class and ethnic group.

Direct examination of the position argued in this thesis

This involves the test of the general hypothesis that a trend in association between ventricle dimensions is a more informative explanation than that yielded by categorical definitions of "enlargement".

Results of the formal case-control analysis for schizophrenia are displayed in Table 3.7a for area measures, and Table 3.7b for volumes. The numbers of controls found in each tertile of the distribution of the LV and third ventricle is shown in the first column of figures in the tables. By definition, a third of the controls fell into each tertile. Had there been no difference between cases and controls, the cases would have been similarly distributed. They were not, as

demonstrated by the increasing odds ratios in the middle and highest tertiles, compared to the lowest.

These raw, unadjusted linear trends were not statistically significant. Once adjustment was made (the next row) for the corresponding intracranial area/volume, the trend became more marked and statistically significant. Adjustment for sex, social class and ethnicity all improved the fit of the logistic regression model significantly, and resulted in a marked increase in the odds ratio for a linear trend in the ventricle size (next row), which remained statistically significant. In Table 3.7a, the adjusted odds ratios for each stratum of maximum LV area in cases versus the control distribution were 1, 2.5 (0.9 - 6.8) and 4.5 (1.5 - 13.3), rather than the raw values of 1, 1.6 and 1.7, indicating why the trend became more marked once the confounding factors were taken into account. There was no evidence of significant interactions; in particular, no evidence that these effects were different in men and women.

Table 3.7a. Odds ratios for tertiles of areas. Schizophrenia cases versus controls

	CONTROLS	SCHIZOPHRENIA CASES			
	N	MAXIMUM LATERAL VENTRICLE AREA		MAXIMUM 3RD VENTRICLE AREA	
		N	OR	N	OR
LOWEST TERTILE	22	29	1.0	30	1
MIDDLE TERTILE	23	44	1.6	39	1.3
HIGHEST TERTILE	22	48	1.7	52	2.0
TEST FOR TREND IN ODDS RATIOS		χ^2=1.98 p=0.2		χ^2=3.36 p=0.07	
ODDS RATIO FOR LINEAR TREND (95% C.I.)		1.3 (0.9 - 1.9)		1.4 (0.98 - 2.1)	
AS ABOVE - ADJUSTED FOR MAXIMUM INTRACRANIAL AREA.		1.5 (1.01 - 2.3)		1.9 (1.2 - 2.9)	
AS ABOVE - ADJUSTED FOR INTRACRANIAL AREA, SEX, SOCIAL CLASS, ETHNICITY & AGE		2.2 (1.3 - 3.7) p=0.005		2.2 (1.3 - 3.8) p=0.005	
OR MODELLED AS CONTINUOUS VARIABLE & ADJUSTED FOR I.C. VOL., SEX, CLASS, ETHNICITY & AGE.		1.1 (1.01 - 1.2) p=0.03 LRS*= 5.3, p=0.02		8.9 (2 - 40) p=0.004 LRS=9.4, p=0.002	

* LRS = Likelihood ratio statistic (Breslow & Day, 1980)

Table 3.7b. Odds ratios for tertiles of volumes.

	CONTROLS	SCHIZOPHRENIA CASES					
	N	LATERAL VENTRICLE VOLUME		THIRD VENTRICLE VOLUME		INTRACRANIAL VOLUME	
		N	OR	N	OR	N	OR
LOWEST TERTILE	22	27	1	31	1	52	1.0
MIDDLE TERTILE	23	49	1.8	42	1.5	49	0.9
HIGHEST TERTILE	22	45	1.7	48	1.6	20	0.4
TEST FOR TREND IN OR		χ^2=1.6 p=0.2		χ^2=1.3 p=0.3		χ^2=3.8 p=0.05	
OR FOR LINEAR TREND		1.3		1.2		0.7	
AS ABOVE - ADJUSTED FOR I.C. VOLUME.		1.6		1.6			
AS ABOVE - ADJUSTED FOR I.C. VOL., SEX, AGE, SOCIAL CLASS, ETHNICITY		1.9 (1.1 - 3.2) p=0.02		1.7 (1.02-2.8) p=0.04		0.8* (0.4-1.4) p=0.4	
OR MODELLED AS CONTINUOUS VARIABLE & ADJUSTED AS ABOVE. REDUCTION IN MODEL DEVIANCE		1.04 (1.02-1.7) p=0.04 LRS=4.9 p=0.043		2.2 (1.04-4.7) p=0.04 LRS=4.6 p=0.03		1.0 (0.9-1.04) p=0.2 LRS=1.7 p=0.2	

* Adjusted for sex, social class & ethnicity.

The final row in Tables 3.7a & 3.7b shows the results from a separate logistic regression analysis where the ventricle size terms were modelled as continuous variables rather than as tertiles. Thus, as the maximum LV area increased by each 1 cm^2, so the odds ratio for cases versus controls having any particular value compared to the previous value, increased multiplicatively by 1.1. For example, cases would be 1.1^{10} (i.e. odds ratio of 2.59) times as likely as controls to have maximum LV area of 150 cm^2, than of 140 cm^2. That there was evidence of a linear trend meant that this effect operated *throughout the range of measured values;* a relationship as in Figure 2.1b or 2.1c was likely, with the gradient defined by the odds for linear trend. There was no evidence of a threshold effect as suggested in Figure 2.1a, or that there would be any bimodality in the distribution of the raw data. The significance of the

likelihood ratio statistic (Breslow & Day, 1980) for total LV measures and third ventricle measures indicated that, in simple terms, regardless of the intracranial volume, sex, ethnicity and social class, these ventricle measures differentiated between cases and controls. The high value of 8.9 for the maximum third ventricle area occurred because this refers to an increase of 1 cm^2 in a structure of mean area 0.5 cm^2, a 200% increase. This problem comparing relative and absolute changes was avoided by the tertile analysis.

Graphical analysis of residuals (Cook & Weisberg, 1982) did not indicate that the relationship between schizophrenia and LV size would be better summarised by a model more complex than a simple, linear trend. Both quadratic and cubic terms were added to the models for lateral and third ventricle dimensions so as to examine for the relationships depicted in Figures 2.1c or 2.1d. There was virtually no improvement in fit of the model, although it is acknowledged that statistical power becomes diminished in these analyses.

When LV and third ventricle volumes were both included in a single regression model, their effects were not statistically independent and remained similar to each other. The two dimensions were highly correlated ($r=0.8$, $p<0.001$); even quite large changes in one would result in predictable change in the other (Armitage & Berry, 1987) and no subject showed great disparity between the two.

The examination of intracranial volume is shown in the final column of Table 3.7b. It appears from the unadjusted odds ratios that there was a significant trend for schizophrenia cases to have smaller intracranial volumes than controls. However, once confounding by socio-demographic factors was controlled, intracranial volume was not a significant discriminator; the smaller intracranial volume in schizophrenic cases was likely to have been secondary to,

although not necessarily caused by, the ethnic composition and the lower childhood social status of this group.

In summary, there was a linear trend for schizophrenic cases to have larger lateral and third ventricles than controls, independently of intracranial size, sex, childhood social class and ethnicity. Intracranial size alone did not differentiate cases from controls.

Schizo-affective Disorder versus controls.

The results for lateral ventricle volume and third ventricle area in schizo-affective disorder are presented in Table 3.8, just as for schizophrenia, and the pattern of results was the same. There were significant trends for the schizo-affective cases to have larger ventricles independent of intracranial volume and other confounders. The effect sizes (magnitude of the odds ratios) were slightly greater than for the schizophrenia group, although the 95% confidence intervals show considerable overlap between the two groups. Closely comparable findings were obtained using LV area or third ventricular volume and, for the sake of brevity, these data are not presented. As for schizophrenia, there was no evidence that a non-linear trend produced a better fit to the data. Thus, in terms of associations with the ventricle sizes, RDC schizophrenia and schizo-affective disorder cases were very similar.

Affective Psychosis versus controls

There was no evidence of an association between LV size and affective psychosis; the distribution of the cases was almost identical to that of the controls, the odds ratios showed no patterns, and none was significantly different from unity. For instance, in the case of total lateral ventricle volume, the adjusted OR for linear trend was only 1.1 (0.65 - 1.9, p=0.7). These results are not tabulated.

See overleaf for Table 3.8

Table 3.8. Lateral Ventricle Volume & Third Ventricle Area. Schizoaffective cases versus controls.

	CONTROLS	SCHIZOAFFECTIVE CASES					
	N	LATERAL VENTRICLE VOLUME		THIRD VENTRICLE AREA		INTRACRANIAL VOLUME	
		N	OR	N	OR	N	OR
LOWEST TERTILE	22	8	1.0	13	1.0	25	1
MIDDLE TERTILE	23	13	1.6	10	0.7	9	0.33
HIGHEST TERTILE	22	19	2.4	17	1.5	6	0.25
TEST FOR TREND IN ODDS RATIOS		χ^2=2.9 p=0.09		χ^2=0.8 p=0.4		χ^2=8.0 p=0.01	
OR FOR LINEAR TREND		1.5 (0.9 - 2.5)		1.4 (0.9 - 2.0)		0.5 (0.3 - 0.8)	
AS ABOVE - ADJUSTED FOR I.C. VOLUME.		2.5 (1.3 - 4.7)		2.6 (1.6 - 4.1)		-	
AS ABOVE - ADJUSTED FOR I.C. VOL., SEX, AGE, SOCIAL CLASS, ETHNICITY		3.3 (1.5 - 7.3) p=0.004		3.4 (1.8 - 6.2) p<0.001		*0.5 (0.2-1.3) p=0.2	
OR MODELLED AS CONTINUOUS VARIABLE & ADJUSTED AS ABOVE. REDUCTION IN MODEL DEVIANCE		1.1 (1.02 - 1.1) p=0.006 LRS=9.2 P=0.002		19 (4.8 - 72) p<0.001 LRS=22.2P<0.001		0.99 (0.9- 1.1) p=0.2 LRS=1.5 P=0.2	

* Adjusted for sex, social class & ethnicity.

This was not the case for the third ventricle in affective disorder (Table 3.9). Increasing third ventricle area (adjusted trend OR=1.8, 95% c.i. 1.1 - 2.8, p=0.01) showed a statistically independent association with affective psychosis. The size of this effect was similar to the other two diagnostic groups, as was the effect size for third ventricle volume (OR=1.5, 95% c.i. 0.8 - 2.6) but the latter was not statistically significant.

Table 3.9 Affective disorder cases versus controls. Third ventricle measures only.

	CONTROLS	AFFECTIVE DISORDER CASES			
	N	MAXIMUM THIRD VENTRICLE AREA		THIRD VENTRICLE VOLUME	
		N	OR	N	OR
LOWEST TERTILE	22	17	1.0	18	1.0
MIDDLE TERTILE	23	15	0.9	13	0.8
HIGHEST TERTILE	22	18	1.2	19	1.1
TEST FOR TREND IN ODDS RATIOS		χ^2=0.2 p=0.8		χ^2=0.02 p=0.9	
ODDS RATIO FOR LINEAR TREND (95% C.I.)		1.2 (0.8 - 1.7)		1.0 (0.7 - 1.6)	
AS ABOVE - ADJUSTED FOR INTRACRANIAL VOL.		1.7 (1.1 - 2.6)		1.4 (0.9 - 2.4)	
AS ABOVE - ADJUSTED FOR INTRACRANIAL VOL., SEX, SOCIAL CLASS, ETHNICITY & AGE		1.8 (1.1 - 2.8) p=0.01		1.5 (0.8 - 2.6) p=0.2	
MODELLED AS CONTINUOUS VARIABLE & ADJUSTED FOR I.C. VOL., SEX, CLASS, ETHNICITY & AGE. OR (95% C.I.)		8.1 (2.4 - 28) p<0.001 LRS=11.9 p<0.001		2.1 (0.9 - 5.1) p=0.1 LRS=2.7 p=0.1	

NB. No evidence of differences between cases and controls for lateral ventricles, anterior horns or intracranial size.

Proportion of variance explained by diagnosis/disease

In view of the similarity of the pattern of effects for schizophrenia and schizo-affective disorder in the above analyses these categories were combined for the following analysis. Table 3.10 shows an example of the multiple regression models used in this stage of the analysis, here examining the proportion of variance in lateral ventricle volume explained by a diagnosis of schizophrenia having adjusted for intracranial volume and sociodemographic factors. The principle was introduced in Chapter 2. Intracranial volume accounts for a significant proportion of the variance in lateral ventricle volume although this is small at 2.6% (change in R^2 0.026). Sociodemographic factors account for a similar proportion of variance (2.3%).

This was not statistically significant but is important to retain in the model so as to allow an un-confounded estimate of the proportion of variance explained by a diagnosis of schizophrenia. This latter proportion was again small at 2.9% but was statistically significant. The total model gave a statistically significant fit to the lateral ventricle data; 13.8% of the variance was explained (see Table 3.11, later). The Durbin-Watson statistic of 1.7 indicated that the residuals were independent rather than following a first order auto-regressive process; the regression model was valid.

Table 3.10 Multiple regression model for proportion of variance of lateral ventricle volume explained by diagnosis of schizophrenia adjusted for intracranial volume and sociodemographic features.

**** MULTIPLE REGRESSION ****

Equation Number 1 Dependent Variable: Lateral ventricular volume

Hypothesis Tests

DF	Sum of Squares	Change in R^2	F	Sig. F	Source
1	386.79	.026	5.5	.02	Intracranial volume
3	343.41	.023	1.6	.18	Sex, ethnic group, social class
1	434.32	.029	6.2	.01	Diagnosis - schizophrenia
5	2040.33		5.82	.0001	Regression
181	12708.64				Residual
186	14748.97				Total

Durbin-Watson Residual Test = 1.7 Range 0 - 4. Values near 2 indicate little autocorrelation of variables

Results for both lateral ventricle volume and third ventricle area (very similar results were obtained for volume) for three diagnostic categories are presented in Table 3.11. In each case

the Durbin-Watson statistic indicated a valid model. The results mirror those obtained from the odds ratio analysis in that while diagnosis explained a slightly greater proportion of variance in third ventricle area than in lateral ventricle volume, there was virtually no explanatory power of affective psychosis with respect to lateral ventricle volume whereas it did explain 2.4% of the variance in third ventricle volume, at borderline statistical significance. The results complement the odds ratio analysis in that they give some idea of the absolute effect size attributable to diagnosis, i.e. small.

Table 3.11 Percentage in variance of lateral ventricle volumes and 3rd ventricle area explained by RDC diagnosis

Diagnosis (n)	Percentage variance explained by diagnosis*		Total variance explained	
	Lateral ventricle volume	Third ventricle area	Lateral ventricle	Third ventricle
Schizophrenia (121)	2.9% F**=6.2 p=0.1	4.6% F=10.6 p=0.001	13.8%	20.6%
Schizophrenia & schizo-affective disorder (162)	4.2% F=10.7 p=0.001	5.7% F=16.0 p<0.001	13.4%	20.3%
Affective disorder (54)	0.5% F=0.6 p=0.4	2.4% F=3.6 p=0.06	10%	24.3%

*Change in R^2 adjusted for intracranial volume, sex, and ethnic group after addition of diagnosis to multiple regression equation.

**F value associated with change in R^2

Extra-cerebral CSF

The distributions of the areas for sulcal fluid, inter-hemispheric fissure and the Sylvian fissures were all highly positively skewed, the modal values being zero, and parametric analysis was not possible. No significant differences between the controls and any of the case groups were

demonstrable with Mann Whitney tests, neither did logistic regression analysis reveal any significant associations, or patterns in the results. This negative result was also found when the global visual ratings were analysed. The difference between left and right sylvian fissure areas (L - R) gave a normally distributed measure of Sylvian fissure laterality (control mean 0.04, 95% c.i. 0.02 - 0.06). There was no association between laterality and any case group versus controls.

Possible determinants of ventricle size - Obstetric complications and family history.

The similarity between the schizophrenic and schizo-affective cases, in terms of the analyses of ventricle size, permitted them to be combined into a single group; the pattern of results was identical for either group alone.

In schizophrenia and schizo-affective disorder combined, definite obstetric complications were slightly more prevalent, but not significantly so, in men than in women (combined diagnoses: men 30% vs. women 22%, OR=1.5, 95% c.i. 0.6 - 4), in higher socio-economic groups (χ^2 trend 1.5, p=0.2) and in white Europeans (OR=2.04 95% c.i. 0.9 - 4.04). In affective disorder, the associations between OC's and sociodemographic variables were similar to the schizophrenia group but none was statistically significant.

Mean volumes of the LV and third ventricles in schizophrenia/schizo-affective disorder and affective disorder cases are shown in Tables 3.12 & 3.13, respectively, broken down by the presence of obstetric complications (OC's; Tables 3.12a & 3.13a) and family history (Tables 3.12b & 3.13b). The F ratios presented in the tables refer to the main effect of OC's or family

history in an ANOVA including age at scan, sex, ethnicity and socio-economic group at birth. The pattern of results was very similar for third ventricle area; for brevity these are not shown.

All schizophrenia/schizo-affective cases, regardless of their OC or family history status showed the pattern of larger ventricles than controls, but the mean lateral ventricle sizes differed between these sub-groups of cases when they were compared with each other. LV volume was smaller in schizophrenia/schizo-affective cases with a history of OC's than in those without, but no significant effect was seen for the third ventricle (Table 3.12a). Those with a positive family history of schizophrenia or schizo-affective disorder also showed this pattern of smaller lateral and third ventricles than those with a negative family history, but this may have been due to chance (Table 3.12b). In all cases, there was no evidence of an association between family history of schizophrenia/schizo-affective disorder and OC's (OR 0.9, 95% c.i. 0.3 - 3.1). When cortical sulci were analysed in terms of visual ratings, no contrast approached statistical significance; the majority (>80%) of cases were judged to have normal or minimally enlarged extra-cerebral spaces whether they were categorised in terms of OC's or the definitions of family history.

In affective disorder, the results regarding cerebral ventricle volumes and OC's were in the opposite direction (Table 3.13a) to the schizophrenia group, although the number of cases with OC's was small. Cases with OC's had significantly larger LV than those without but, as in the schizophrenia group, no effect was seen for the third ventricle. Differences for family history (Table 3.13b) were small and not significant. There was no evidence that these effects were different in men and women when interaction terms were examined in the ANOVAs.

Table 3.12a Obstetric complications and ventricle size in schizophrenia and schizo-affective disorder cases (n=162).

		OBSTETRIC COMPLICATIONS	
		ABSENT N=87	PRESENT N=34
TOTAL LATERAL VENTRICLE VOLUME (MEAN VOLS. CM^3)	UNADJUSTED	21.2	18.3
	ADJUSTED**	21.8	17.1
	F RATIO	F=4.9 p=0.03	
THIRD VENTRICLE VOLUME (MEAN VOLS. CM^3)	UNADJUSTED	1.05	1.0
	ADJUSTED**	1.07	0.95
	F RATIO	F=0.9 p=0.3	

Table 3.12b Family history and ventricle size in schizophrenia and schizo-affective disorder cases.

		FAMILY HISTORY OF SCHIZOPHRENIA OR SCHIZO-AFFECTIVE		FAMILY HISTORY OF AFFECTIVE DISORDER		FAMILY HISTORY OF ANY FH-RDC DISORDER.	
		ABSENT N=138	PRESENT N=24	ABSENT N=123	PRESENT N=39	ABSENT N=87	PRESENT N=75
TOTAL LATERAL VENTRICLE VOLUME (MEAN VOLS. CM^3)	UNADJUSTED	20.6	16.8	19.8	20.9	20.3	19.8
	ADJUSTED**	20.8	16.7	20.1	20.4	20.4	19.9
	F RATIO	F=2.5 p=0.1		F=0.1 p=0.8		F=0.01 p=0.9	
THIRD VENTRICLE VOLUME (MEAN VOLS. CM^3)	UNADJUSTED	1.06	0.84	0.98	1.18	0.98	1.08
	ADJUSTED**	1.07	0.80	0.99	1.15	0.99	1.08
	F RATIO	F=3.5 p=0.06		F=2.7 p=0.1		F=1.4 p=0.2	

* Includes FH-RDC cases of schizophrenia, schizoaffective disorder, bipolar disorder, unipolar depression, other psychosis, suicide & psychiatric disorder N.O.S.

** Mean value adjusted for intracranial volume, age, sex, social class & ethnicity. Multiple classification analysis method.

Table 3.13a Obstetric complications and ventricle size in affecive disorder cases (n=54)

		OBSTETRIC COMPLICATIONS	
		ABSENT N=32	PRESENT N=7
TOTAL LATERAL VENTRICLE VOLUME (MEAN VOLS. CM^3)	UNADJUSTED	18.0	27.7
	ADJUSTED**	16.0	27.4
	F RATIO	F=6.2 p=0.02	
THIRD VENTRICLE VOLUME (MEAN VOLS. CM^3)	UNADJUSTED	0.92	1.25
	ADJUSTED**	0.95	1.18
	F RATIO	F=2.1 p=0.1	

Table 3.13b Family history and ventricle size in affective disorder cases

		FAMILY HISTORY OF SCHIZOPHRENIA OR SCHIZO-AFFECTIVE		FAMILY HISTORY OF AFFECTIVE DISORDER		FAMILY HISTORY OF ANY FH-RDC DISORDER.	
		ABSENT N=48	PRESENT N=6	ABSENT N=39	PRESENT N=15	ABSENT N=33	PRESENT N=21
TOTAL LATERAL VENTRICLE VOLUME (MEAN VOLS. CM^3)	UNADJUSTED	17.7	21.9	19.5	14.7	18.9	17.0
	ADJUSTED**	17.0	21.3	18.8	14.1	17.8	17.0
	F RATIO	F=1.02 p=0.3		F=1.4 p=0.2		F=0.1 p=0.8	
THIRD VENTRICLE VOLUME (MEAN VOLS. CM^3)	UNADJUSTED	0.93	1.04	0.98	0.85	0.94	0.96
	ADJUSTED**	0.94	1.04	1.02	0.78	0.96	0.93
	F RATIO	F=0.2 p=0.6		F=1.2 p=0.3		F=0.03 p=0.9	

* Includes FH-RDC cases of schizophrenia, schizoaffective disorder, bipolar disorder, unipolar depression, other psychosis, suicide & psychiatric disorder N.O.S.

** Mean value adjusted for intracranial volume, age, sex, social class & ethnicity. Multiple classification analysis method.

Clinical correlates of ventricle dimensions in Schizophrenia and Schizo-affective disorder.

Chronicity

The general pattern of associations between lateral and third ventricle volumes, and schizophrenia and schizo-affective disorder was unchanged when the analyses were restricted to first admissions (n=47). For instance, for schizophrenia alone (compare Table 3.7b), restriction of the analysis to cases scanned during their first admission resulted in an unadjusted OR for linear trend in the association between LV volume and schizophrenia of 1.2, and of 1.4 for third ventricle volume. There was no large or significant correlation between ventricle volume and either number of previous admissions or weeks as an in-patient prior to index admission. Two further measures of chronicity were investigated. Firstly, the time from first contact with psychiatric services until CT scanning was calculated. There was no evidence of a significant association with LV volume or 3rd ventricle area, either in a simple scatter plot or in a multiple linear regression model controlling for intracranial size, sex, social class and ethnicity. Secondly, for subjects other than those scanned during their first admission to hospital, the proportion of time since first contact spent as an in-patient was calculated and analysed in the same way. Once again, no association was evident between ventricle dimensions and this composite chronicity-severity variable.

Age at onset

There was no evidence in simple scatter plots of a significant negative association between age at onset and LV volume for either sex. In fact, the regression lines indicated a weak positive relationship (men, age at onset = 0.08 x LV volume + 20, p=0.3); younger onset was associated with smaller ventricles. This was explored further using a multiple regression model including sex, social class, ethnicity and intracranial volume. Sex remained the only significant variable,

having a coefficient of 3.5 (t=2.7, p=0.007); females had a later age at onset regardless of ventricle size or social characteristics.

Premorbid social adjustment

No associations were demonstrated between premorbid social adjustment and ventricle dimensions in the total psychosis group, or in any diagnostic groups alone. This negative finding was unaffected by the method of analysis; unadjusted ventricle volume did not correlate with premorbid social adjustment (r=-0.1, p=0.4), neither did ANOVA controlling for head-size, sex, ethnic group or social class reveal evidence of an association between premorbid social adjustment and lateral ventricle volume (F=0.2, p=0.8).

Referral bias

This was not a sample from a readily definable population at risk, although the place of residence was known and all subjects came from London but that is a heterogeneous place. In an effort to define whether there was any bias from tertiary referrals with severe illness from outside the catchment area, the analyses of trends in the association between lateral ventricle volume and maximum third ventricle area were repeated for only those subjects with schizophrenia living in the two health districts served by the hospitals involved (n=88, 72.7%). For brevity, the results are not tabulated. In summary, the results and effects were very similar as in the whole sample shown in Tables 3.7 a&b. The odds ratios for LV volume modelled as a continuous variable and adjusted for confounding was unchanged at 1.04 although the confidence limits were wider (1.1 - 2.0) reflecting the smaller sample. There was no evidence of referral bias having been an explanation for the results. Sampling only those subjects with a living parent as an informant will have biased the sample towards those of younger age at onset but, within this group, there was no evidence that this will have caused a systematic bias. Replication in a population-based sample would be the only way of addressing this, as it would be for assessing the effect of the sampling method for controls.

Discussion

The main argument of the thesis was supported. The analytical approach has avoided and perhaps begun to resolve the confusion over the considerable overlap between ventricle size in cases and controls, and the problem of defining 'enlargement'. The results demonstrated that, regardless of sex, age, intracranial volume, social class or ethnicity, cases with schizophrenia or schizo-affective disorder are *more likely* than controls to have larger ventricles. For affective psychosis, this effect appeared to be confined to the third ventricle. The amount of variance explained by diagnosis was small so these effects are operating in a subtle manner, in terms of size of structures - effects at a microscopic level may be much more dramatic. Within the diagnostic case groups, obstetric complications were significantly associated with smaller lateral ventricles in schizophrenia, and larger ventricles in affective psychosis; this was against any prior hypothesis.

Methodological Issues

It is unlikely that cases were biased towards those having particularly large ventricles. The majority of local cases of schizophrenia are admitted to hospital and the minority who are not, differ little from those who are (Castle et al., 1993), a finding confirmed in Scotland (Geddes & Kendell, 1995). An attempt was made to collect CT scan data on all cases eligible, and there is no reason to believe that subjects who refused to have a scan were a special group in terms of ventricle size. The sample comprised mainly of cases from local catchment areas but also included tertiary referrals, perhaps more likely to have severe illness and larger ventricles; there was no evidence of this but it remains a possible bias. However, the sample was far from a true, population-based study. It is unlikely that the results here are due to this fact but it is acknowledged that confirmation of the findings in such a study would strengthen them greatly.

Population-based or not, the cross-sectional nature of the survey raises the possibility that chronic cases with large ventricles influenced the results. The finding of no association between ventricle size and chronicity of schizophrenia was evidence against this. In accordance with the view that age-related ventricle changes make appreciable impact only after 50-60 years (Zatz et al., 1982; Pfefferbaum et al., 1988; Stafford et al., 1988; Pearlson et al., 1989), age correction made no difference to the results in this study, where 97% of the subjects, including affective psychotics, were under 50 years,

Regarding possible confounding by ethnicity, restriction of the analysis to white Europeans was not feasible due to the high proportion of cases from other ethnic groups, predominantly Afro-Caribbeans. It was assumed that the non-white controls were representative of these ethnic groups, and to control for confounding using the regression methods described. Further interesting analyses were possible regarding ethnicity within the case groups alone. However they would be tangential to the thesis; a control group with a large enough number of non-white European subjects, particularly Afro-Caribbeans, would have allowed the hypothesis to be tested that the nature of the associations demonstrated between schizophrenia and ventricle dimensions were the same (or different) in this population, an important question given the debate over the nature of the epidemic in this population.

Lack of control data regarding family history and obstetric complications prohibited the investigation of interactions between these putative aetiological variables and ventricle dimensions; the hypothesis that the associations demonstrated mediate any effect only when a third variable is present cannot be ruled out. However, as discussed later, the analysis of these variables in the case group alone makes this unlikely, but by no means impossible.

No adjustment was made for verbal intelligence. Both intellectual function and psychosis are undoubtedly linked to brain structure; to have matched for cerebral function in terms of IQ might have obscured the association of interest between psychosis and ventricle size (Gur et al., 1991; Resnick, 1992; Jones et al., 1993a; Jones & Rodgers, 1993). Also, the case groups included individuals where English was not the first language. This may have reduced the estimated IQ.

Despite its drawbacks, this study has some strong points. It is based upon one of the largest series of CT scans in the functional psychoses (Takahashi et al., 1981; Sacchetti et al., 1992), and there was an attempt to minimise patient selection bias by including all suitable consecutive admissions. Automated CT image analysis will have reduced measurement error. Clinically, each patient was assessed in depth, with an independent informant where possible. The controls were a volunteer sample, not "super-normal" and allowed the control of common confounders in the analysis. Lastly, the use of an analysis based on the population distribution has heuristic value and may point the way to an explanation of the baffling overlap between case and control distributions.

Findings

The main argument of the thesis

The results of testing the main hypotheses in this study supported the thesis. The most important results came from the odds ratio analysis of ventricle size in cases and controls. Although the notion of large ventricles is widely accepted in schizophrenia, the analysis allowed more to be concluded than just a statement of a significant group differences in mean values. Firstly, since it generated a level of risk, or probability, the result from each comparison can be expressed in a universal quantity (odds ratio) which can be compared in

magnitude to quite different aetiological factors such as the season of birth effect (OR approx. 1.1) and genetic predisposition (OR approx. 10). Secondly, and for the same reason, it also allows relative weight to be given to different anatomical abnormalities; both LV and third ventricular enlargement in schizophrenia carried odds of approximately 2.0 and should be given equal priority in further attempts to understand their origin; schizophrenia explained a similar (small) proportion of the variance of each across the range of values. Thus, with structural MRI, if the odds for temporal horn enlargement or cerebral asymmetry in schizophrenia greatly exceeded that for the overall LV, present efforts to concentrate more on the former (DeGreef et al., 1992) would be justified.

Thirdly, the finding of a significant linear trend across the three tertiles indicated that the association between schizophrenia and ventricle size was not confined to a subgroup of cases with very large ventricles; in that case the odds would have been increased just across the upper tertile. This was in agreement with results from frequency distribution analyses (Harvey et al., 1990b; Daniels, 1991; Vita et al., 1996). These studies used statistical techniques to test whether or not a distribution would be best described by one, two or more distributions. None found evidence of bimodality within case groups alone, and that of Vita (1996) suggested that the mixed population of cases and controls was best described by two distributions, indicating that the schizophrenia cases *as a group* were all shifted towards having larger ventricles.

The results were also in agreement with studies of both discordant monozygotic twins (Reveley et al., 1982; Suddath et al., 1990) and sibling pairs (Weinberger et al., 1981; DeLisi et al., 1986). In these studies, affected cases did not represent a homogeneous subgroup of brain structural abnormality but were merely each predictably different from their twin or sibling. These findings are mentioned again in the general discussion in Chapter 5.

Thus, the overlap between the ventricle sizes of cases and controls (Shelton & Weinberger, 1986; Iacono et al., 1988; Birley, 1992) may be explained, and the problems of defining "enlargement" avoided. The increased risk conferred by increasing ventricle size is not confined to those with the largest ventricles, it is continuous throughout the population. The findings of overlap in distributions of ventricle size and the lack of evidence in favour of bimodality cease to be a puzzle in this framework; they are to be expected, as is the corollary, that most subjects with schizophrenia will have ventricle size within the normal range. Indeed, the ultimate conclusion from these strands of evidence would be that it is not a sub-group, but all people with schizophrenia who have enlarged ventricles: each case has slightly larger ventricles than expected, had they not had schizophrenia.

Finally, the increase in odds ratio observed for, and the proportion of variance explained by schizophrenia were both modest; ventricle size is a statistically independent risk factor which operates throughout the population range, but one of moderate size. The association should be judged as very unlikely to be a direct causal one, and it can readily be seen that type II errors might be common in smaller samples.

The control group confirmed both the well established, normal gender difference in intracranial volume, and the entwined influences of IQ, social class and cranial size - a problem that remains unresolved in structural MRI research (Andreasen et al., 1990b; Zipursky et al., 1991; Andreasen et al., 1993; Chua & McKenna, 1995). There was no demonstrable difference in cranial size between cases and controls once adjustment was made for sociodemographic factors. I do not interpret the finding of a relationship between head-size, social class and IQ within the controls as sufficient evidence of cause and effect. On the contrary, there is evidence of a strong relationship between social advantage and general body dimensions (Tizard, 1975) which may be quite independent of that between social class and educational

achievement. This raises the possibility that similar confounding occurs in neuropathological studies and suggests that more attention should be given to the relationship between sociodemographic characteristics and brain structure on a cytoarchitectural level. Regarding differences between men and women, an *a priori* decision was made to test for gender differences in the association between ventricle size and RDC psychoses by fitting "sex*ventricle size" interaction terms in the logistic regression models. None approached statistical significance and it may be concluded that there was no evidence that the associations demonstrated between cases and ventricle dimensions were different in men and women.

Structural brain changes in affective disorder have received less attention in the literature than is the case for schizophrenia. In this study, subjects with affective psychotics showed no evidence of LV enlargement in either men or women, but were significantly more likely than controls to have large third ventricles. The diagnosis explained a significant, though small proportion of the variance in third ventricle area but had virtually no explanatory power for the lateral ventricle. Although some earlier CT studies strongly implied that there was LV enlargement in patients with affective illness, this has not been a consistent finding (Scott et al., 1983; Dolan et al., 1985; Schlegel & Kretzschmar, 1987; Andreasen et al., 1990c) and has become increasingly uncertain with recent MRI reports (Johnstone et al., 1989; Swayze et al., 1990; Coffey et al., 1993). The affective patients in this sample all had positive psychotic symptoms, previously associated with greater structural change (Scott et al., 1983; Targum et al., 1983; Lutchins et al., 1984; Sacchetti et al., 1987; Schlegel & Kretzschmar, 1987), so one might conclude that the absence of LV enlargement is all the more convincing. This is particularly so, given that the diagnostic misclassifications with schizo-affective disorder and schizophrenia would be more likely in such a group.

In regard to third ventricle size in affective psychosis, previous CT results have been similarly inconsistent (Schlegel & Kretzschmar, 1987; Dewan et al., 1988; Iacono et al., 1988, reviewed by Elkis et al., 1995). The marked discrepancy between the lack of association with LV size and the definitive association between affective disorder and increasing third ventricle size indicates this was a real phenomenon; it was not that, in a small sample, one result was statistically significant whereas the other just fell short. In a MRI study, Coffey et al., (1993) demonstrated that subjects with affective disorder referred for electroconvulsive therapy had both larger lateral (18%) and third ventricle (6%) volumes, although the results for their sample (n=47) were not significant. They commented that their data were compatible with a 3rd ventricle volume increase of up to 30% indicating that the present results are not contradictory. Their effects were corrected for educational status which, I believe, would have been an additional reason for their best estimate to be biased towards the null.

It is likely that structural changes do occur in affective psychosis but over a more restricted area (primarily the diencephalon) than in schizophrenia. In terms of risk, it is possible that such changes, betrayed by large third ventricles, are relevant to psychosis in general, rather than to any particular diagnosis. As discussed in chapter 1 when the views of Rothman (e.g. Rothman, 1982) were considered, this lack of specificity to schizophrenia does not rule out its being closely related to causation. Studies on larger, more representative samples of affective disorders, including milder forms, would be useful here in that predictions could be made as to how associations would change as the case mix varied. However, this study indicates that attention would best be diverted away from LV size in affective disorder if abnormalities are proving so elusive (Coffey et al., 1993).

Correlates of ventricle size

In contrast to the findings in the formal case-control analysis, the results were less clear regarding correlates of ventricle size within the case groups alone, just as Lewis concluded was the case in his review of studies undertaken during the 1970's and 1980's (Lewis 1990).

The absence of an association between duration of illness and ventricle size is important, and supports results from first episode CT studies (Turner et al., 1986) and four follow-up studies (Nasrallah et al., 1986; Illowsky et al., 1988; Reveley et al., 1988; Vita et al., 1988). Nasrallah and colleagues demonstrated considerable variability in VBR at the second, follow-up scan, possibly a consequence of the smaller "sample" of measures used in studies of area, compared with studies using volumes calculated from several slices. Two recent MRI studies employing volume measurements (Degreef et al., 1991; DeLisi et al., 1992) support this contention and the finding of lack of progression, although the later study continues to be followed-up and to recruit subjects so final conclusions are awaited. The importance of the apparent lack of association between LV volume and chronicity shown to date lies in the implication that the determinants of the size are active early in life and by inference, that the modification of risk for schizophrenia also occurs early.

Of the studies looking for an association between family history and ventricle size, five have reported an inverse correlation between ventricular size and positive family history (Reveley et al., 1984; Cazullo et al., 1985; Turner et al., 1986; Romani, 1987; Owen et al., 1989). One study found a positive correlation (Nasrallah et al., 1983) and one evidence of a curvilinear correlation (Owens et al., 1985). Most reports have found no relationship (Pearlson et al., 1985; Farmer et al., 1987; Kemali et al., 1986; Nimgaonkar et al., 1988; Johnstone et al., 1989b; Pearlson et al., 1989; Kaiya et al., 1989; Reddy et al., 1989; Andreasen et al., 1990a).

The present investigation, like other studies, relied on the family history method, with the inherent likelihood of misclassification, and had no data for normal controls. It did have available a larger sample size than all the negative studies. The present results offer little support for the inverse relationship in schizophrenia between family history of the disorder and ventricle size, and no support for the hypothesis that a family history of affective disorder may be associated with small ventricles in schizophrenia (Owen et al., 1989). However, as mentioned in the introduction to this chapter, Murray and Jones (1996) have recently demonstrated that sex may be a important effect modifier in the relationship between family history and ventricle size, although the lack of interaction in the current analysis indicates that sex does not modify the relationship between the latter and schizophrenia. Perhaps different aetiologies act differentially on the sexes (Castle and Murray, 1991) although the final common pathways to disease are similar, betrayed here crudely by altered ventricle size. Further work in this area would be certainly enhanced if more sophisticated methods of scoring family history such as those developed by Sham and colleagues (Verdoux et al., 1996; Duggan, 1995) were used.

The lack of normative control data hinders interpretation of the contrary findings regarding OC's and ventricle volume in schizophrenia and affective psychosis. It is most unlikely that OC's might have opposite effects on LV volume in the two conditions, particularly as there was no evidence of an effect on the third ventricle in either diagnostic group. Just as for family history, presence or absence of OC's is likely to represent a crude classification of early environmental risk factors, and the most parsimonious conclusion from the data is that the nature of the true associations between such factors and ventricle volume remains unclear (Lewis, 1990). Recent studies (Kendell et al., 1996; Jones et al., 1996; Verdoux et al., 1996b) indicate certain perinatal events, particularly those involving hypoxia, as being primary. A

further tranche of work in this sample will be use the results of these studies as definitions of OCs. Prospective studies where cases and controls have been followed since birth and are available for structural neuro-imaging in adult life - or ideally during childhood - may solve the question once and for all, and are now becoming feasible (Isohanni et al., 1996). The key will be to have complete data on cases and controls in order to be able to test more complex models and interactions, particularly between brain structure and function, and putative aetiological factors.

Chapter Summary

The finding in the late 1970's of large cerebral ventricles in schizophrenia was instrumental in re-establishing a biological approach to the condition. This phenomenon is now widely accepted but the considerable overlap of dimensions between those with schizophrenia and controls has not been resolved in the literature and continues to cause debate. It is good example of a risk factor for a chronic disease where the majority of those affected have normal values and the majority of the population with high values remain unaffected by disease. Examination of the relationship between schizophrenia and ventricle size was the first test presented of the thesis that the notion of a continuous risk factor, rather than of categorical, "either - or" risks, better explained the true situation in schizophrenia. The specificity of this with respect to affective psychosis was examined.

This chapter described an examination of the argument set out in Chapter 2 in the context of a case-control study of volumetric computerised tomographic scan measures in 216 consecutive admissions for functional psychosis and 67 healthy community controls. The main hypothesis was that there would be a trend in the risk for schizophrenia associated with ventricle size with no evidence of a threshold effect. Odds ratio analysis demonstrated significant linear trends in the association between increasing lateral and third ventricle volumes, and both RDC schizophrenia (n=121) and schizo-affective disorder (n=41); cases were consistently associated with larger volumes than controls. There was an association between larger third, but not lateral, ventricle size in affective psychoses (n=54). These associations were statistically independent of intracranial volume, sex, social class and ethnicity, factors which were significantly associated with ventricular measures in the controls, i.e. confounders.

There was no evidence of a threshold corresponding to the notion of normal versus enlarged ventricles. The results were consistent with the possibility that the majority of cases of schizophrenia and schizo-affective disorder had some degree of ventricle enlargement. This was also the case in affective disorder for the third ventricle.

Having established this, the question as to whether other putative risk factors would be associated with ventricle dimensions was posed. Within the schizophrenia group, there were no large or significant associations between ventricle dimensions and age at onset, duration of illness or premorbid social functioning. Neither obstetric complications nor a family history of schizophrenia or other psychiatric illness was associated with larger ventricles.

Chapter 4

Childhood motor milestones, IQ and social behaviour prior to adult schizophrenia.

An examination of categorical versus continuous risks in a British birth cohort: The MRC National Survey of Health & Development

Introduction

This chapter examines the main argument of the thesis in terms of the relationship between events in early life and adult onset schizophrenia. The questions of whether early risks apply to the minority or the majority is posed; evidence is sought in favour of the *possibility* of the latter.

It appears that several common, chronic diseases of adulthood may have their origins in the first few months of life. The importance of such remote risk factors for adult physical illnesses such as ischaemic heart disease and diabetes has become apparent only relatively recently (Barker et al., 1989; Barker et al., 1990; Godfrey et al., 1993). Proposed mechanisms are diverse and include fetal programming of continued physical growth (Poskitt & Cole, 1977; Lucas, 1991), and infections, both *in utero* (Fine et al., 1985) and in childhood (Pullen & Hay, 1982).

Continuities between early factors and adult psychological morbidity have been accepted for considerably longer, and exploration of possible mechanisms for the link has given rise to a variety of explanatory models. These include the straightforward continuity of behaviour seen between childhood conduct disorder and adult antisocial personality disorder (Robins, 1966; Rutter & Giller, 1983), continuity both of intrinsic (e.g. personality) and of extrinsic risk factors from childhood through to adult life, or the persistence of personality characteristics which lead to behaviours placing individuals at risk of mental illness (Rodgers, 1990 a&b; Rutter, 1984).

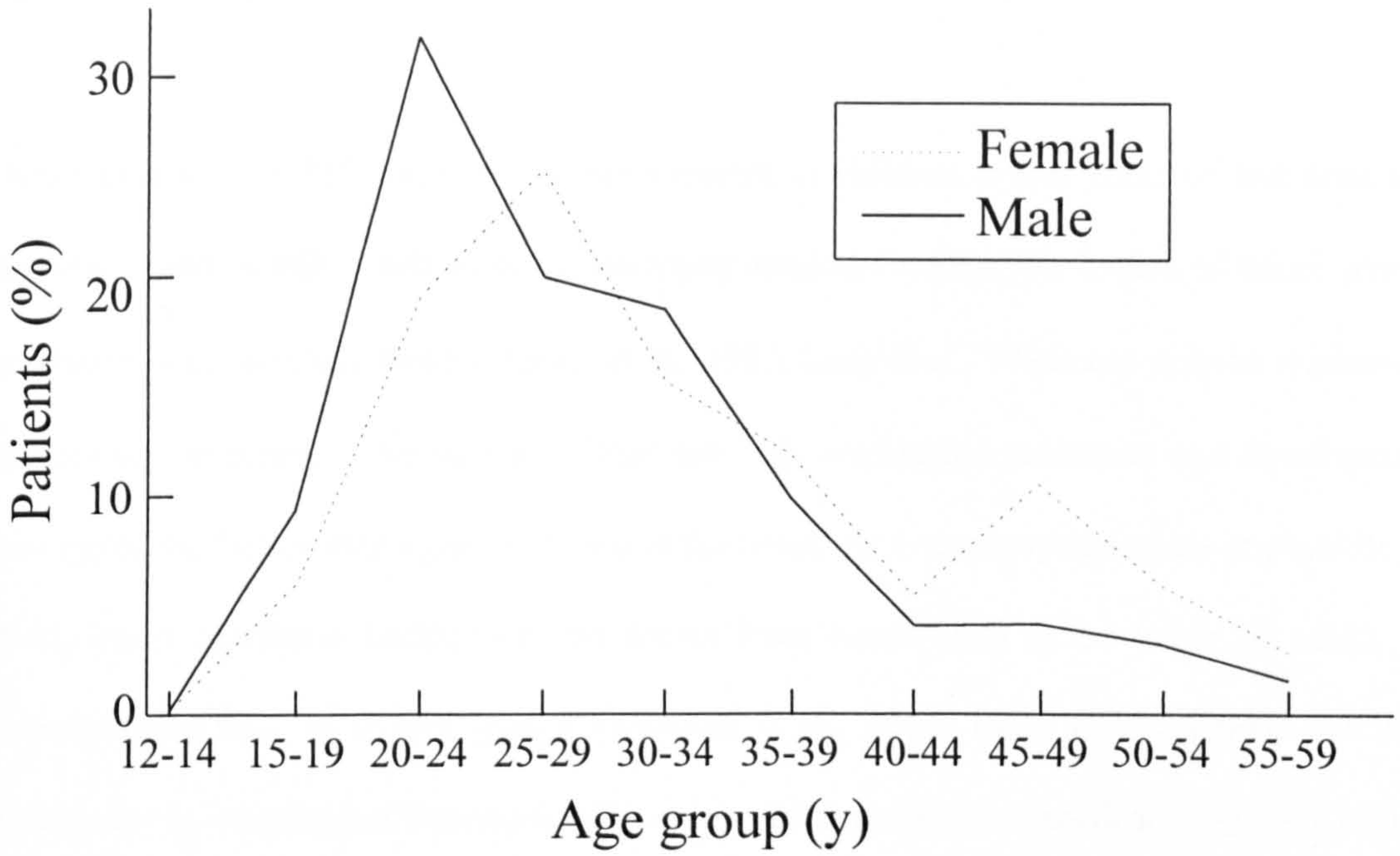
Adult onset schizophrenia as a developmental disorder

Schizophrenia has long been linked to childhood psychological abnormalities (Kraepelin, 1896; 1919) such as social awkwardness and withdrawal (Watt, 1978) although these are quite different from the hallucinations, delusions and thought disorder which characterise schizophrenia, particularly as defined by the operational diagnoses used in the studies described here. The

question remains open as to which of the models of continuity outlined above best describes this situation. More biological explanations tend currently to favour a modified version of the first of those models described above: early and late psychological abnormalities being manifestations of the same underlying brain lesion, the *normal* development of surrounding brain areas and their corresponding functions having a pathoplastic effect on those manifestations (Weinberger, 1987). This is the fundamental version of the neurodevelopmental hypothesis of schizophrenia (Murray & Lewis, 1987).

In Chapter 1, the notion of schizophrenia as a largely cross-sectional, clinical syndrome was proposed. There is a characteristic association between age and the emergence of this clinical, psychotic syndrome, regardless of the detailed differences between classification systems and exactly how onset is defined. Figure 4.1, taken from work by Hafner and colleagues (Hafner et al., 1993), shows the frequency distribution of ages at onset. There are reliable differences between men and women (Hafner et al., 1993) but, for either sex, the association between age and incidence is striking and suggests a *prime facie* case for schizophrenia being related to the life course and being, in some sense, a developmental disorder. The clinical formulation of this as developmental, rather than degenerative process depends largely upon whether there are abnormalities or differences demonstrable before the onset of the schizophrenia syndrome. Some have proposed (e.g. Castle et al., 1994) that the age at onset distribution itself subsumes 2 or three separate distributions, particularly a later onset group occurring mainly in women, a possibility illustrated well in Figure 4.1. The great majority of subjects with schizophrenia appear to lie in the main body of the distribution scattered around the first mode. It is most likely that it is to them that the neurodevelopmental *sub-group* model applies. They comprise the majority of subjects in empirical research and parsimony might suggest that this majority in both sexes would share similar constellations of causes with some pathoplastic effect of sex on the age at onset.

Figure 4.1 Distributions of age at onset of schizophrenia. From Hafner et al., 1993



Corroborative evidence for an early event comes form diverse sources. Histopathological studies of adults with schizophrenia indicate that developmental processes may have gone awry in some areas, particularly in the formation of hippocampal structures (Roberts, 1990) and the frontal cortex (Akbarian et al., 1993 a&b). Some findings have proved difficult to replicate, although there is, presumably, some microscopic basis to the macroscopic structural differences which have been demonstrated in neuroimaging studies of schizophrenia (see Chapters 3 & 5). As noted in Chapter 3, pregnancy and delivery complications have been found to be more common in the histories of adults with schizophrenia than controls in many (O'Callaghan et al., 1990; Lewis et al., 1989; Buka et al., 1993; Kendell et al., 1996; Jones et al., 1996) but not all studies (Done et al., 1991) and, if there is a true association, its nature and the direction of causality is a matter of debate (Goodman, 1988; Sacker, et al., 1995). Similarly, there is evidence of an association in populations between schizophrenia and prenatal exposure to influenza (Mednick et al., 1988; Sham et al., 1992; but see also Crow, 1992; Crow & Done, 1992; Selten & Slaets, 1994;

Erlenmeyer-Kimling et al., 1994; Susser et al., 1994), and maternal malnutrition (Susser & Lin, 1992; Susser et al. 1996).

Direct evidence of differences in the development of children is less common but does exist. Although there is still debate as to the neuropathological findings, the excess of minor physical anomalies seen in schizophrenia (Green et al., 1987; Lane et al., 1996) can only be explained in developmental terms. The skin and brain are both ectodermal structures and developmental damage to the former may signal problems in the latter. At a more psychological or physiological level, mean childhood intelligence test scores have been found to be lower in adults with schizophrenia than in control groups (Aylward et al., 1984; Done et al., 1994), and subtle differences in neurological development have been demonstrated in genetically high risk children and in those not known to be so (Fish, 1977; Erlenmeyer-Kimling et al., 1982; Walker & Lewine, 1990; Fish et al., 1992). It is these developmental effects, together with behaviour, which are considered empirically in this chapter.

Given so many strands of evidence pointing to very early developmental events as being involved in schizophrenia, possibly involving the early determination of brain structure (Jones and Murray, 1991), why study the intervening psychological and neurological events any further? Why not concentrate on possible causal factors at early stages in development and the processes which are involved with the precipitation of psychosis in later life? There is the plain argument of accrual of knowledge; any explanation of schizophrenia must also explain its characteristics as they emerge over time. Accurate and precise description of pre-psychotic traits is a pre-requisite to identification of high risk individuals, facilitating early diagnosis and prompt treatment. The latter has been shown consistently to affect prognosis (May et al., 1976; 1981; Huber et al., 1980; Crow et al., 1986; Lieberman et al., 1992) and is an important and realistic aim. Early prediction may one day allow prevention. Such goals will rely on the accurate characterisation of the traits

preceding psychosis, and of the true nature of the distribution of the risk within the population (Rose, 1992). Prevention is discussed further in Chapter 5.

Unfortunately, demonstrating such associations between early events and a disorder with onset most commonly in the third or fourth decade of life is problematic. Retrospective designs are prone to recall biases resulting in spurious associations and the less obvious problem of subtle but important effects remaining undetected due merely to the vagaries of memory. Often, the best that can be achieved is a classification of complex early characteristics as either present or absent, normal or abnormal; the subsequent consideration of the nature of the risk conferred is similarly dichotomised (Gittleman-Klein & Klein, 1969; Cannon-Spoor et al., 1982; Watt & Lubensky, 1976; Done, et al., 1994). It is hypothesised in this chapter that this leads to a "false dichotomy" and an inadequate explanation of the distribution of risk, just as was demonstrated in Chapter 3 for cerebral ventricle dimensions.

Few studies in this area have had population controls available with most relying on the demonstration of differences in group means, leading to further emphasis on the idea of 'abnormality' versus 'normality' arbitrarily defined, as well as to lack of comparability between studies. In general, evidence of childhood developmental deviance, defined as either present or absent, in around one third of adults with schizophrenia has given rise to the notion that these individuals have a distinct subtype of the disorder. If the early characteristics were defined in fine detail in population-based samples, then evidence of a familiar dose-response relationship may be revealed, just as is the case with many risk factors for chronic disease. This chapter aims to shed light on the question as to whether early developmental events are involved in the minority or majority of schizophrenia; aetiology may be diverse, acting through homogeneous developmental mechanisms. Thus, the chapter is an account of a further examination of the thesis under different conditions.

Longitudinal studies of general population samples are one of the best ways of investigating the questions outlined above, although these, too, have their problems; large samples are required to yield adequate numbers of cases and the childhood information, whilst unbiased, is often not ideally suited to the purpose. In Britain there have been three such studies with suitable childhood data in which the participants have lived through any or all of the period of risk for psychosis; the three birth cohort studies of 1946, 1958 and 1970. In this chapter an analysis in the first of these, the Medical Research Council National Survey of Health and Development, is presented. Much of the work has been done in parallel to separate investigations into the childhood behavioural antecedents of schizophrenia which have been undertaken in the 1958 British birth cohort by John Done, Tim Crow, Eve Johnstone and Amanda Sacker (Done et al., 1994), in addition to their work on obstetric events (e.g. Done et al., 1991). Many of their findings have provided important evidence to support the notion of development going awry prior to adult schizophrenia. However, the research group has pursued a different line of argument from that presented in this thesis. John Done and I have compared and contrasted findings regarding individual developmental characteristics in the two cohorts (Jones & Done, 1997). These findings are very similar, particularly for IQ, but the comparison has no direct bearing on this thesis.

Hypotheses are tested regarding timing of motor milestones, level of intelligence and behavioural characteristics in children destined to develop schizophrenia as adults. The hypotheses state that these characteristics are best described not as excessively "abnormal", as would be predicted by the contemporary neurodevelopmental hypothesis and routine practice in psychiatric research, but as continuous risk factors for the illness. The data available allowed emphasis on the distribution of risks within the population, rather than concentrating on cases alone.

Methods

Sample

The study sample was drawn from the Medical Research Council National Survey of Health and Development (NSHD). This is a stratified, random sample (n=5362) of a survey of births in England, Scotland and Wales during the week 3-9th March 1946 (RCOG, 1948). The original survey, comprising 13,687 mothers, was carried out due to concerns over a fall in the birth rate (which proved unfounded) and in order to collect information intended for use in planning for the National Health Service which would be introduced in 1948 (Wadsworth, 1987).

Following a decision championed by Dr James Douglas and colleagues, the present sample was followed-up. Data on this cohort, described elsewhere extensively (Atkins et al., 1981; Wadsworth, 1991), were collected on 11 occasions before age 16 years and, so far, on 9 thereafter. All interviews were undertaken by interviewers specially trained for the survey sweeps, mainly health visitors and nurses.

The risk set (i.e. survey members at risk of being identified as schizophrenic in adulthood) used in this investigation comprised all subjects alive and living in the U.K. at age 16 years (n=4746).

Identification of cases.

Cases of schizophrenia with onset between ages 16 and 43 years, when the most recent NSHD interview occurred, were defined by the author using a two stage screen. This aimed at high specificity (low proportion of false positives in the cases), rather than high sensitivity (high proportion of true positives identified as cases).

The first stage identified all survey members for whom there was any evidence to suggest schizophrenia, severe unclassified mental illness, unspecified psychiatric hospital admission or use of prescribed neuroleptic drugs, using the following sources.

- The 9 questionnaire and interview contacts made between 16 and 43 years of age made enquiries into all hospital in- and out-patient contacts, general practice visits, and recorded survey members' own descriptions of their illnesses and prescribed neuroleptic drug use.

- Appearances in the Mental Health Enquiry (MHE) for England and Wales which were identified up to age 36 years, and up to age 44 for the Scottish MHE. These data were independent of follow-up by the National Survey.

- A short version (Rodgers & Mann, 1986) of the Present State Examination (PSE; Wing et al., 1974) administered at age 36, which included probe questions for psychosis.

In the second stage, DSM-IIIR (APA, 1987) operational criteria for schizophrenia or schizo-affective disorder were applied by the author to all clinical material on survey members thus identified, blind to all information collected between birth and 16 years. Clinical information was available from a variety of sources including abstracted details of mental state during admissions and from complete case notes. The former, and sometimes the latter, were supplied by hospitals in response to routine requests by the NSHD whenever a hospital admission had been identified and for those who responded positively to probes for psychosis in the short PSE. Survey members also described their symptoms during the routine interviews.

In order to investigate the effect of diagnostic misclassification, cases of schizophrenia were divided according to the certainty of diagnosis. Group 1 comprised those fulfilling DSM-III-R criteria for schizophrenia or schizo-affective disorder. Group 2 comprised those where positive DSM-III-R criteria were fulfilled, but where no definitive statement could be found of relevant exclusions. For example, positive schizophrenic phenomena were described, but affective symptoms were not mentioned and so could not be excluded conclusively as being predominant.

Age at onset was defined as the age at which a case was first seen by a psychiatrist or, when unavailable, the age at which NSHD records first indicated a psychiatric problem.

Controls

Control subjects were defined as the entire risk set, excluding those identified as cases of schizophrenia.

Selection of childhood variables of interest.

Guided by the existing literature on antecedents of adult schizophrenia and wishing to avoid multiple comparisons and type 1 statistical errors, variables referring to the period prior to age 16 were selected for analysis in the following domains:

- socio-demographic - socio-economic class & sex ,with particular reference to confounding by these factors.
- physical and neuro-developmental, e.g. sexual maturity & motor milestones
- cognitive e.g. educational attainment test scores
- socio-behavioural e.g. mothers' and teachers' comments on behaviour.

Those in the first domain were identified (and confirmed) as confounders of the relationship between schizophrenia and the other three, domains the thesis being examined in relation to these three. Where possible, individual variables were selected where data existed for more than one age enabling assessment of developmental change. Variables examined, together with their derivation, are summarised in the Appendix to this chapter.

Statistical analysis.

The general strategy outlined in Chapter 2 and used in Chapter 3 is used. Frequency distributions of age at reaching milestones and I.Q. were plotted so as to examine overlap between cases and controls, followed by calculating differences between mean values and 95% confidence intervals (95% c.i.). Principal components analysis (Pearson, 1901; Manly, 1986) was used to reduce the complexity of educational test data, where several tests had been administered at each age, and for early milestones.

The existence of sub-groups of particularly "abnormal" cases of schizophrenia analogous to a developmental sub-type of the disorder was investigated in a similar way to that employed in Chapter 3, following a brief consideration of major confounding factors. Some presentations are truncated so as to avoid duplication of the argument.

For IQ and developmental milestones the plan was as follows. Firstly, frequency distributions of milestone and IQ scores were simply examined by eye for evidence of bimodality in the case group, and the variances and standard deviations compared. Frequency distributions of IQ were examined using a single, 6.8% random sample of controls (n=300) so as to facilitate computing

and the preparation of graphs; regular software will not accommodate more data. Sampling was performed only once using the SPSS-PC procedure "sample".

Next, the analysis concentrated on the population at risk of the disorder in order to ascertain whether cases arose from a particular sub-group of the population, as defined by motor milestones and IQ scores. Just as for cerebral ventricle dimensions in Chapter 3, initial analysis concentrated on applying a statistical definition of abnormality to the milestone data (after principle components analysis) and IQ scores which, by definition, were normally distributed within the population and particularly suitable to this treatment. As before, abnormality was defined as 1 and then 2 standard deviations above the control mean. The distributions of these scores were then divided by their tertiles into thirds, based upon the control data. Logistic regression analysis was used to calculate the relative risk (as odds ratios) of cases arising from each section of the distribution, and to account for confounding by sex and social class of origin.

The specific hypothesis was tested of a trend in the association between risk of schizophrenia and motor milestone and IQ test score (i.e. a dose-response relationship between score and risk), as opposed to high risk of the disorder being confined to a particular section of the population. This hypothesis was that this trend would be inverse, i.e. later milestones, lower IQ related to higher risk of schizophrenia. However, all hypothesis tests were 2 tailed so as to give the most conservative results and avoid chance findings. All comparisons were adjusted for confounding by sex and socio-economic status (s.e.s.) which was defined on the basis of father's occupation.

The proportion of the variance in age at reaching early developmental milestones and in IQ score which might be explained by a diagnosis of schizophrenia was defined.

Attention was then turned to behavioural ratings, again contrasting categorical and continuous measures. The validity of using quantitative analyses of qualitative data is questionable: the analysis is presented for heuristic value.

Finally, there was a consideration of the case group in terms of the possibility of a sub-group defined in terms of several variables at once. Correlations between developmental characteristics were compared in cases and controls so as to investigate whether a tighter correlation in the cases might b a manifestation of a developmentally deviant sub-group. A group deviant at age 2 years and at age 15 was identified and the risk of schizophrenia was defined and risk of schizophrenia in this group identified.

Results

There were 2477 men (52.2%) in the risk set of 4746 survey members. There were 81 survey members for whom there was evidence, up to age 43 years and eight months, of a diagnosis of schizophrenia, use of regular neuroleptic medication, undefined severe mental illness or a psychiatric admission for unknown cause. Of these, 30 (20 male) met DSM-IIIR criteria for schizophrenia or schizo-affective disorder, with 22 (73%) falling into the more confident diagnostic group. Together, these were the "cases of schizophrenia" for this analysis.

Risk of schizophrenia up to age 43 years was 30/4746 = 0.63% (95% c.i. 0.41 - 0.86%). The risk for men (0.81% 95% c.i. 0.45 - 1.2) was greater than that for women (0.44%, 95% c.i. 0.17 - 0.71; OR 1.8, 95% c.i. 0.9 - 3.9).

Social class at birth of survey member is shown in Table 4.1. There was a trend for higher social class in the cases, but this was small and non-significant (χ^2 trend 2.5, p=0.1).

Table 4.1. Occupational group of father at birth of survey member.
Trend for higher status in cases.

Socio-economic group at birth	Cases	Controls	Odds ratio vs. I & II (95% c.i.)
I & II	9	1077	1
III non-manual	9	1149	0.9 (0.3 - 2.6)
III manual	8	1262	0.8 (0.3 - 2.2)
IV & V	4	1214	0.4 (0.1 - 1.4)

χ^2 test for trend 2.5 p=0.1

Age at onset of schizophrenia

The mean age at onset of schizophrenia in the risk set was 24.3 years (95% c.i. 21.5 - 27; median 21.5 years; range 17 - 43 years). Men had an earlier mean age at onset (23.4 years; 95% c.i. 19.8 - 27.1) than did women (25.9 years; 95% c.i. 21.6 - 30.2).

Early developmental milestones

The mean ages at which speech and gross motor milestones were reached was consistently later for the cases than for controls (Table 4.2), particularly for walking (cases 1.2 months later, 95% c.i. difference 0.1 - 2.3 months later, p=0.005). Standard deviations for cases and controls were similar for each.

At age 2 years, survey members who had not yet reached all their milestones were identified. There was an excess of cases over controls in this group, compared with the group where all milestones were seen by the health visitors to have been attained (2/25 cases versus 64/3854 controls; OR=4.8, χ^2=5.4, p=0.02); speech was the milestone not attained in both these cases.

Table 4.2. Age at reaching developmental milestones.

Milestone	Case modal value*	Control mean* (s.d.)	Case-control difference* (95% ci)
Sitting	6	6.5 (1.5)	0.1 later (0.5 earlier - 0.8 later)
Standing	12	11.4 (2.2)	0.2 later (0.6 earlier - 1.0 later)
Walking	12	13.5 (2.4)	**1.2 later** (0.1 later - 2.3 later)
Teething	6	6.8 (2.2)	0.2 earlier (1.0 earlier - 0.6 later)
Talking	18	14.3 (4.2)	1.2 later (0.4 earlier - 2.8 later)

* months

Correlations between the ages of the individual milestones in the entire risk set (Table 4.3) indicated that the motor milestones of sitting, standing and walking were all, as expected, related. Correlations with talking were much smaller, and smaller still with teething, a milestone about which there were no prior hypotheses. Based on this correlation matrix, the timings of motor milestones and talking were subjected to principal components analysis with a forced solution of two factors; loadings are shown in Table 4.4. The first factor appeared to be a measure of general motor development and was used as such in later analyses. The second factor comprised almost entirely the age at which the children spoke, as defined above. For simplicity, further analyses used the raw age at talking score, rather than the latent variable. Inspection of the frequency distributions of the raw scores indicated that they were all affected by recall bias, even at age 24 months. There was "terminal digit preference" in that mothers had preferentially recalled even numbered months as the age at which milestones were reached. For the motor milestones principle components analysis tended to lessen this effect on the distribution (but not the bias) and so this composite milestone variable was subjected to further analysis for evidence of a linear trend.

Were the predicted differences in milestones presented in Table 4.2 due to a sub-group of abnormal cases or to a smaller but more widespread effect amongst the pre-schizophrenic children? Figures 4.2 and 4.3 show the distributions of scores for the motor factor and for talking, respectively, using the random sample of 300 controls. The scatter-plot for motor milestones (Figure 4.2) indicated that, for the schizophrenia data, it was possible that the mean value was disproportionately influenced by a minority of cases, but there was no evidence of a discrete sub-group. Logarithmic or other transformations was unhelpful and were not used, as per the analysis of CT data (Chapter 3). Standard deviations for cases and controls were 1.3 and 0.98, respectively, although the variances were not unequivocally distinct ($F=1.63$, $p=0.07$).

Table 4.3 Correlations between milestones in entire risk set (subjects with complete data)

	Sitting	*Standing*	*Walking*	*Teething*	*Talking*
Sitting	1.0	.46**	.44**	.15**	.12**
Standing	.46**	1.0	.81**	.06**	.15**
Walking	.44**	.81**	1.0	.07**	.15**
Teething	.15**	.06**	.07**	1.0	.10**
Talking	.12**	.15**	.15**	.10**	1.0

N of cases: 3912 2-tailed Signif: * - .01 ** - .001

Table 4.4 Loadings onto two developmental milestone 'factors' or principal components of milestone data.

	Factor 1	*Factor 2*
Sitting	.33	-.01
Standing	.43	-.04
Walking	.43	-.04
Talking	-.08	1.01

Factor 1 betrays general motor development. Factor 2 comprises almost entirely talking.

Figure 4.2 Motor milestone factor score in cases and controls

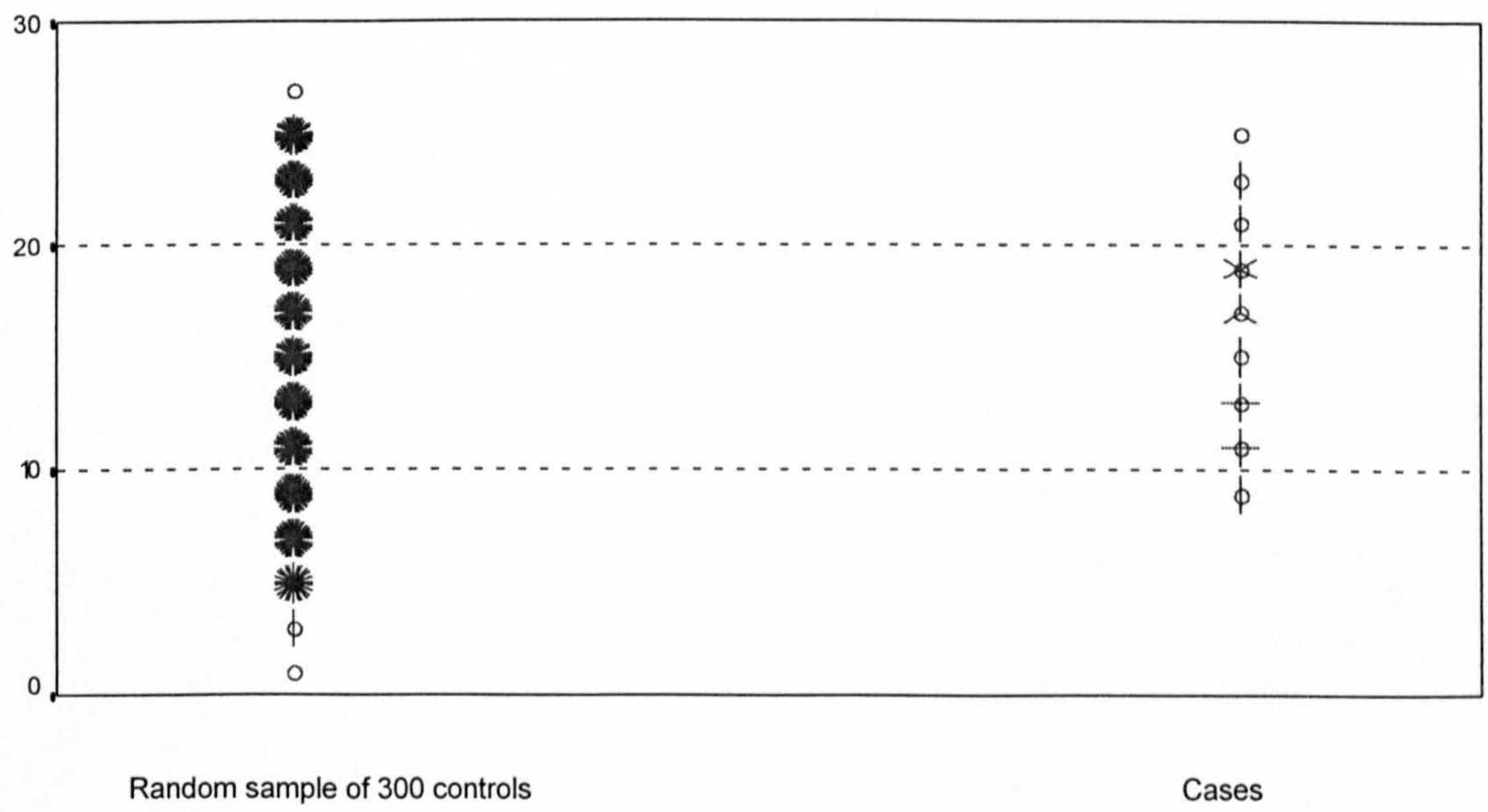


Figure 4.3 Age at talking in cases and controls

Data for age at talking are displayed in Figure 4.3 which uses a "sunflower" plot in order to display multiple occurrences of data points, the number of petals being proportional to the number of subjects. Here the impression is of the whole distribution of scores in the cases being shifted towards later ages, although a ceiling effect is apparent for both groups, the data being collected around the age of two years. Standard deviations were very similar for cases and controls (4.5 vs. 4.2) with the underlying variances being virtually indistinguishable ($F=1.1$, $p=0.7$).

This approach did not take account of confounding. Of the data available social class and sex were the most likely confounders, both related to risk of schizophrenia (v.s.). Both were also related to the motor milestone factor and to age at talking. Results are shown in Table 4.5a & Table 4.5b.

Table 4.5a Association in controls between sex and motor milestone factor in controls (n=4154).

	Mean score for age at talking (months)	Difference (95% c.i. difference)
Boys	14.8	1.0 month; (0.7, 1.2); p<0.001
Girls	13.8	

Table 4.5b Association in controls between social class and age at talking in controls.

	Mean score for age at talking (months)	Analysis of variance
Social class 1 & 2	15.0	F=10.4 p,0.001
Social class 3N	14.0	
Social class 3 M	14.1	
Social class 4 & 5	14.2	

The categorical approach was the next stage to examining the thesis and, in view of the above analysis, account was taken for confounding of effects by social class and sex. Would the data be adequately explained by the prevalence of scores one or two standard deviations above the control mean of age at talking and of the motor milestone factor? These means were, 14.3 months (s.d. 4.2) for talking and, by definition, zero (s.d. 1.0) for the motor milestone factor.

Table 4.6 shows the prevalence of these categorical definitions of late milestones; the Table is analogous to Table 3.3, and the message is similar although the predictable effect of adjusting for confounding is different in that all effects are adjusted towards the null.

Table 4.6 Association between schizophrenia and late attainment of milestones defined in two ways: Later than one, and later than two standard deviations above the control mean: the categorical approach. P values > 0.1 are not shown.

	Percentage (No.) cases with late milestones*	Raw Odds Ratio (95% c.i.)	Adjusted OR** (95% c.i.)
Talking later than 1 s.d of control mean	20.0% (6)	2.1; 0.8, 5.1; p=0.1	1.9; 0.8, 4.7; p=0.1
Talking later than 2 s.d. of control mean	3.3% (1)	1.2; 0.2, 8.9	1.1; 0.1, 8.0
Motor milestone factor 1 s.d. above control mean	20% (6)	1.8; 0.7, 4.3	1.6; 0.6, 3.9
Motor milestone factor 2 s.d. above control mean	10% (3)	3.1; 0.9, 10.2 p=0.1	2.7; 0.9, 9.0; p=0.1

* By definition, approx. 16 % & 2.5% of controls would have values above 1 and 2 standard deviations, respectively, above the population (control) mean.

** Odds ratio adjusted for social class and sex.

The slightly later talking appeared to be accounted for by an excess of cases between 1 and 2 s.d. from the mean. The effect did not reach 95% confidence but as a prior hypothesis, it was quite likely to reflect a true effect. Effects for the motor factor were slightly more marked, again in line with the hypothesis but just failing to achieve 95% confidence. The three-fold increase in prevalence of scores in the top 2 s.d. of the control distribution certainly did indicate an association between later attainment of motor milestones and schizophrenia. However, if this

were related to some causal mechanism acting through a developmental process, as defined it would be operating in only a tiny minority of schizophrenia leaving the rest excluded from this explanation. A sub-type could be invoked to explain this but would this be correct? Would the development test of a linear trend in the association between schizophrenia and attenuated provide a possible explanation relevant to a greater proportion of schizophrenia?

The distributions of age at talking and the motor milestone score were divided by their tertiles into thirds and a linear trend in the association between presence in these categories and schizophrenia was tested, as a raw effect and following adjustment for confounding by sex and social class. the Results are included for completeness and as an illustration of where the format of testing thesis is not successful.

Results are displayed in Tables 4.7a & 4.7b. For clarity, p values and confidence limits are not included as the message is clear; no evidence was found of any effects at all, let alone a trend. However, there are some problems with these data due to the multiple modes and terminal digit preference noted above. It was not possible to divide the distribution of age at talking into anything like true thirds although the odds ratio analysis should have accounted for this if there were any effect to find. The difference in mean scores was small and any "shift" could not be defined by the relatively crude division into thirds. The differences in means, particularly for the motor factor may well have been particularly influenced by outliers but the data from the health visitors at age 2 shows that these could not have been extreme as all children who were to develop schizophrenia were walking by then.. Division of the distribution into finer categories, e.g. by its quartiles, in order to investigate this further is hampered by the small numbers of cases. Modelling the factors as continuous measures in logistic regression models resulted in no improvement in the fit of the models to the data and, as expected from Tables 4.7 a&b, not a hint of a trend.

Table 4.7a Age at talking divided by earliest "third" of the population, middle third & latest third. χ^2 trend 0.85 p=0.5.

	Earliest	*Middle*	*Latest*
		OR* 0.75	OR* 1.4
		Adjusted** OR 1.0	Adjusted OR 0.8
Cases (n=26)	6 (23.1%)	8 (30.8%)	12 (46.2%)
Controls (n=4154)	996 (24%)	1770 (42.6%)	1388 (33.4)

* Compared with earliest as baseline ** Adjusted for social class and sex

Table 4.7b Motor milestone factor score divided by earliest "third" of the population, middle third & latest third. χ^2 trend = zero.

	Earliest	*Middle*	*Latest*
		OR* 1.0	OR* 1.0
		Adjusted** OR 1.0	Adjusted OR 1.1
Cases (n=28)	10 (35.7%)	9 (32.1%)	9 (32.1%)
Controls (n=4185)	1557 (37.2%)	1228 (29.3%)	1400 (33.5%)

* Compared with earliest as baseline ** Adjusted for social class and sex

Cognitive Test Scores

There were a large number of educational test scores and a priority in order to test the general thesis was to simplify them. However, individual scores were examined first in terms of their means as they are of intrinsic interest. The hypothesis was that mean scores would all be lower in children who would develop schizophrenia, with some evidence in the literature that the greatest effect would be for non-verbal scores (Aylward et al., 1984).

Mean, unadjusted scores in the individual educational tests at ages 8, 11 and 13 years are shown in Table 4.8. Confirming the first hypothesis in the previous paragraph, cases scored consistently lower than the controls in all tests, at all three ages and across all sub-scores. In general, this pattern of the differences between the means, together with the confidence limits, suggested that deficits in the scores of the cases were most marked for verbal, non-verbal and mathematical skills, and least for reading and vocabulary. The hypothesis that non-verbal abilities would be preferentially affected was not supported, although all scores were highly correlated in cases and controls making a single deficit in group means highly unlikely.

Principal components analysis of normalised scores resulted in a single factor, the first principal component (PC 1), analogous to a "G" score. This factor explained some 75% of the variance in scores at each age and comprised similar (0.72 - 0.91) contributions from each sub-test. Mean values of PC 1, were lower in the cases than controls at age 8 (difference = 0.3 s.d., 95% c.i. -0.1 to 0.7), age 11 (difference = 0.2 s.d., 95% c.i. -0.1 to 0.5) and at 15 when the gap had widened (difference = 0.48 s.d., 95% c.i. 0.1 to 0.9).

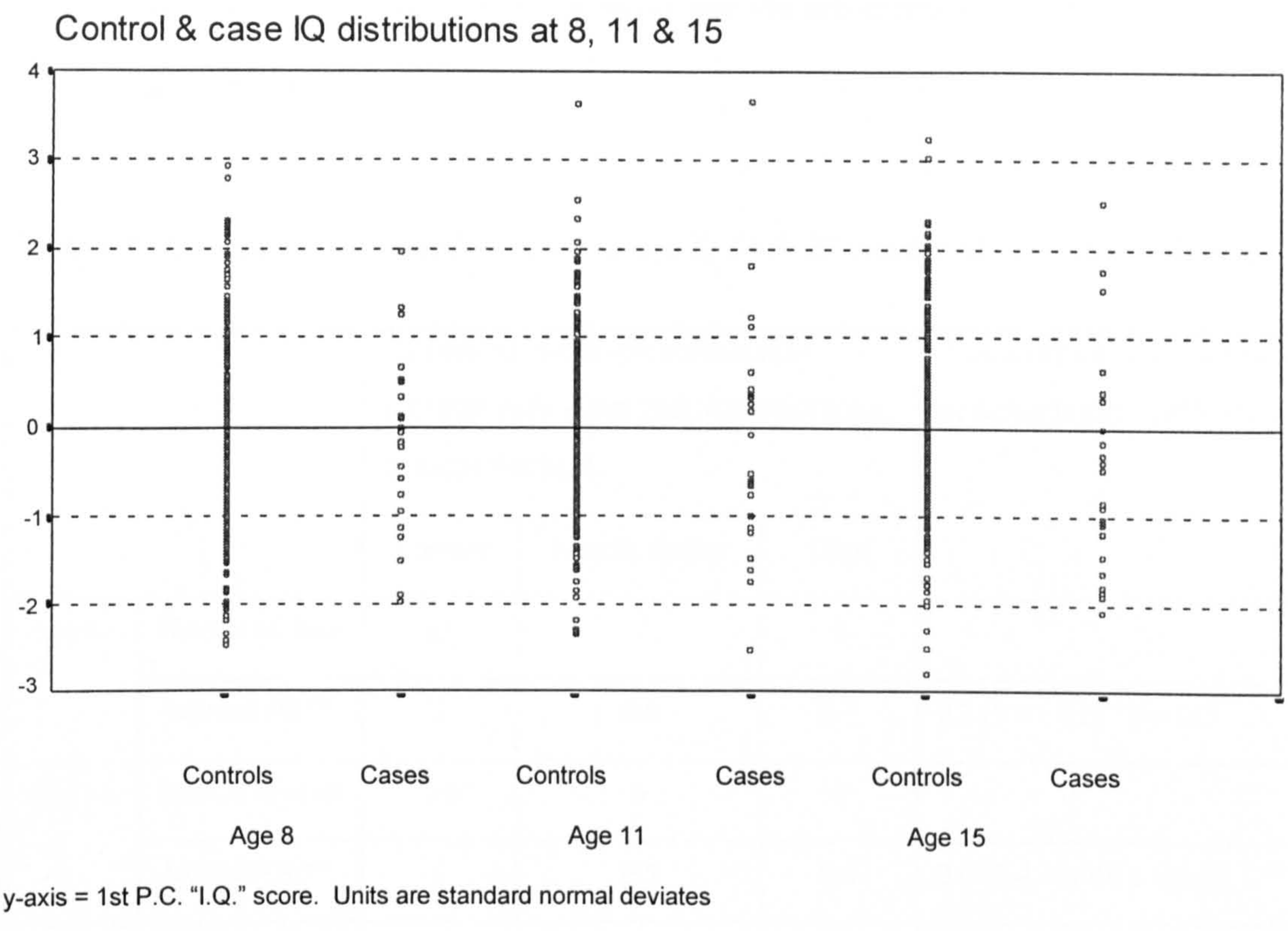
Table 4.8 Mean deficits shown by cases in educational test scores at ages 8, 11 and 15 years. Normalised scores based on NSHD population mean 100, std. dev. 15.

Test of ability	AGE (YRS)	CASE MEAN (STD DEV)	MEAN DEFICIT SHOWN BY CASES* (% 1 S.D.)	F RATIO**	P
Non-verbal	8	97.0 (14.1)	5.9 (39%)	3.8	0.05
	11	98.9 (16.7)	4.4 (29%)	2.1	0.14
	15	93.6 (15.9)	9.5 (63%)	9.9	0.002
Verbal	8	96.6 (15.4)	7.1 (47%)	5.7	0.02
	11	97.3 (15.8)	5.2 (35%)	3.3	0.07
	15	96.3 (12.5)	7.5 (50%)	6.5	0.01
Arithmetic / Mathematics	11	97.6 (16.4)	6.1 (41%)	5.1	0.02
	15	99.2 (13.6)	6.9 (46%)	5.7	0.02
Vocabulary	8	100.8 (17.7)	3.1 (21%)	1.1	0.3
	11	99.8 (14.6)	4.5 (30%)	2.3	0.2
Reading	8	99.6 (16.3)	4.0 (27%)	1.8	0.2
	11	100.1 (14.6)	4.5 (30%)	2.3	0.2
	15	100.2 (12.7)	3.5 (24%)	1.5	0.2

* Corrected for confounding by sex & social class using multiple classification analysis. Risk set means >100 due to differential sampling of NSHD.

** ANOVA - main effect of case vs. control. No gender by case interaction was significant.

Figure 4.4 shows the distributions of IQ scores for controls and cases side by side at each age. No sub-group of cases with particularly low IQ appeared to be accounting or the discrepancies in scores. Scores for the majority of cases were within two standard deviations of the mean value for the controls plotted on the y axis, although scores above the mean were relatively less common than below it. The impression was that cases became more frequent within the distribution at progressively lower scores.



y-axis = 1st P.C. "I.Q." score. Units are standard normal deviates

Single random sample of 300 controls

Fig. 4.4 IQ scores at 3 ages

The plan of analysis in the thesis dictated that the first stage involved a categorical measure of "low IQ", such as the prevalence in cases and controls of scores more than 1 or 2 standard deviations below the control mean. The hypothesis would be that such scores would be more common. Learning from the previous examples of frequency distributions, the pattern of the mean scores and similar categorical analyses in this chapter and from Chapter 3, the clear hypothesis at this stage would be that the prevalence of such a statistical definition of "low IQ" might be more common after adjusting for confounding but that the effect would not apply to the vast majority of children who will develop schizophrenia and the vast majority of (the minority) of children who are defined as of low IQ will never develop psychosis. Inspection of Figure 4.4 shows that there were virtually no cases with scores 2 standard deviations below the mean - none at age 8, one at age 11 (score -2.54), and one (a different subject, score -2.08) at age 15. There

seemed little point in making such a tabulation and the arguments of the thesis was examined further without this step.

Table 4.9 Association between IQ score at age 8, 11 & 15 years and later schizophrenia.*

		IQ TERTILE BASED ON POPULATION DISTRIBUTION (ONE THIRD OF CONTROLS IN EACH TERTILE)			SUMMARY OR FOR LINEAR TREND IN ASSOCIATION (95% C.I.)
		Lowest	Middle ability	High	
Age 8	Number of cases	11	7	6	
	Adjusted OR**	1	0.6	0.5	0.7 (0.4 - 1.2) p = 0.2
Age 11	Number of cases	14	6	6	
	Adjusted OR**	1	0.5	0.4	0.6 (0.4 - 0.99) p = 0.04
Age 15	Number of cases	13	8	4	
	Adjusted OR**	1	0.6	0.3	0.5 (0.3 - 0.9) p = 0.01

* 1st principal component derived from all scores at any age.

** Adjusted for confounding by sex and social class. One third of controls in each tertile. Lowest ability as baseline odds.

The IQ distributions were divided by their tertiles into thirds, based upon the control data (Table 4.9), as described above. The raw data form the body of the tables with the bottom line being a summary odds ratio adjusted for sex and social class, obtained from logistic regression. This represents the increased odds of developing schizophrenia if a score is in the middle tertile versus the highest group, or the lowest versus the middle. Similar results were obtained using quartiles but occasional empty cells prohibited analysis. There was no evidence that a non-linear trend (e.g. quadratic) gave a better fit to the data, nor was there evidence of an interaction with gender; girls and boys were very similar.

The impression from the initial investigation of differences in mean values was confirmed but there was also a clear pattern in the adjusted odds ratios. Cases were consistently over-represented in the lowest third of the test scores, even at age 8, after which the effect appeared to become more marked. Logistic regression was used to further analyse these repeated measures, taking into account sex, social class, and the effect of previous score. Inclusion of the 1st PC score at age 15 into a model containing sex and social class resulted in a significant improvement in the fit of the model (reduction in deviance; likelihood ratio statistic (LRS) = 7.7, p = 0.005). Addition of the score at age 11 resulted in a slight decrease in deviance (LRS = 1.3; p = 0.5) and change in the odds ratio associated with the 15 year score (OR=0.59, p = 0.03). Similarly, addition of score at age 8 resulted in a tiny improvement in the fit of the model (LRS=0.6; p = 0.7) associated with a change in the odds ratio associated with the 15 year score which remained statistically significant (OR = 0.64; p = 0.04). There was no evidence of effect modification by sex; with the statistical resolution of the study, IQ effects for girls and boys were similar.

The most parsimonious conclusion from the statistical model outlined above is that the majority, or even all of the children destined to become cases of schizophrenia showed a slight decrement in observed IQ thus shifting the entire distribution and being reflected in a lower group mean. Unfortunately, the division of the distribution into thirds, rather than more divisions, was relatively crude and it was possible that the observed effect was due to a minority of the cases with very deviant scores, just as for the milestones. This is discussed below. Again, inspection of the frequency distributions of IQ scores for cases and controls at each of the three ages was informative and indicated this was unlikely.

If low IQ were a risk for schizophrenia, would it be related to age at onset? There was no evidence of an association between these two variables within the case group, either alone (IQ at

15; r = -0.14, p = 0.5) or when corrected for sex and social class in a multiple regression equation (beta = -0.11, p = 0.65). However, power was very low when analysing only the 30 cases and the safest conclusion here is that such a correlation could not be defined with any meaningful precision; the 95% confidence limit for the raw correlation between I.Q. and age at onset was wide (-.64 - +.46).

Proportion of population variance in IQ explained by schizophrenia

Lastly, the proportion of variance explained by a diagnosis of schizophrenia was quantified, as for cerebral ventricle size in Chapter 3, Table 3.10; the table is not repeated. Once sex and social class were accounted for, each of which accounted for approximately 1% of the variance in IQ at each age and were highly significant, schizophrenia accounted for 0.05% at age 8 (one twentieth of one percent), 0.02% at age 11 and 0.2% at age 15. At only the last of these ages was the effect of diagnosis statistically significant (F=7.1, p=0.01) being nowhere near so at earlier ages.

Thus, although schizophrenia had a statistically significant effect on the variance in IQ at age 15, and changes in IQ carried a demonstrable relative effect, the absolute size of this effect in terms of the total variation in IQ seen in the population was tiny, being of no practical significance for the population whatsoever. This was as expected; the IQ of a population is not determined by the prevalence of a relatively rare condition like schizophrenia even if the effects within that condition are marked, and risk of that rare condition is related to IQ.

In conclusion, general ability was adequately summarised by the PC 1 at each age and this score was lower in cases than controls. The deficit between cases and controls became statistically significant at 15 and remained so when account was taken of regression to the mean in a logistic regression model. Cases tended to score below the controls at all three ages - the lower the IQ

score, the greater the risk (odds) of becoming a case, regardless of sex or social class. There was no evidence of a sub-group of cases with very low scores nor that cases arose solely from a sub-group of the population with low IQ. The effect of schizophrenia in the population on population IQ is of statistical significance but of no practical significance.

Social and behavioural characteristics

Social and behavioural characteristics of children destined to develop schizophrenia were the last factors against which the validity of the thesis was judged. The situation here was different from ventricle size, timing of milestones or IQ. These factors are clearly valid, continuous variables. Making them categorical loses information and the question as to whether there is a threshold effect on risk versus a continuous increase in risk summarised by a trend is clear.

Behavioural ratings may not be truly continuous and so categorical ratings may be quite valid, albeit that some psychological theories posit underlying behavioural or personality dimensions, such as Eysenck's extraversion/introversion and neuroticism which determine individual behaviours which are then judged present or absent. Furthermore the validity of applying quantitative methods to even these dimensions has been questioned (Macnaughton, 1996) in the drive to develop valid qualitative methods for behaviour. Such scales are not necessarily ordinal; moving from zero to three on a scale of anxiety might not mean anything similar to moving from four to seven.. If these are considered as risk factors for other behaviours (e.g. schizophrenia) the notion of a threshold in effect is of questionable validity. Still, it makes an interesting situation in which to examine the thesis, particularly as the data available are relevant to some of the original behavioural features described by Kraepelin (1896) as pre-dating schizophrenia.

The hypotheses were that behaviours characterising the shy, schizoid habit described by Kraepelin would be risk factors for schizophrenia. Research in the 1958 birth cohort (Done et al., 1994; Jones and Done, 1997) indicated that boys who would develop schizophrenia may be particularly likely to show naughty, "externalising" behaviours. An attempt was made to replicate this. Furthermore, where continuous measures of these traits were available it was hypothesised that there would be a trend in risk - the more they were present in an individual, the greater the risk of that individual developing schizophrenia in adult life. The thesis was that such a formulation would be a more complete explanation of the distribution of risk that was possible with the categorical scores.

Thus, play preferences and behavioural ratings were analysed first as categorical, present or absent ratings, then using continuous scales, as described in the Appendix to this chapter.

Play preference at ages 4 and 6 predicted schizophrenia (Tables 4.10a & 4.10b). At both ages, children who displayed a preference for playing alone were more likely to become cases (age 4, OR = 2.1, p = 0.05; age 6, OR = 2.5, p = 0.05). Numbers of siblings and ages of siblings did not differentiate cases from controls.

Table 4.10a. Play preference at ages 4.

	Plays alone	Plays with others
Cases	10	20
Controls	876	3840
Odds ratio- crude & adjusted*	2.2 (1 - 4.9), p = 0.04; 2.1 (0.9 - 4.7), p = 0.05	

*sex & social class

Table 4.10b. Play preference at ages 6.

	Plays alone	Plays with others
Cases	5	25
Controls	355	4361
Odds ratio- crude & adjusted*	2.5 (0.8 - 6.6), p = 0.06; 2.5 (0.8 - 6.9), p = 0.05	

*sex & social class

Teachers' comments at ages 13 and 15 years

At ages 13 and 15, teachers indicated that the children destined to be cases exhibited several behaviours more commonly than controls. Results are displayed in Table 4.11 and Table 4.12 for each age, respectively. Some items are noted at only one age due to data being unavailable from the NSHD. Crude odds ratios refer to the effect in the schizophrenia group as a whole, followed by the effect size (OR) in girls and boys, separately. The final column for each age is the effect size adjusted for confounding by gender. These results need to be interpreted against the finding that, when given the opportunity to single-out individuals as mal-adjusted or problem-children, no teacher identified a child who developed schizophrenia. Thus, all the effects discussed below were likely to have been subtle, even in combination.

There appeared to be strong evidence of a constellation of "anxious", "solitary" behaviours to be noted by teachers when the children were both 13 and 15 years, when different teachers would have rated them. Both girls and boys were *tired and "washed-out"* in class, *avoided rough games and competition* with other children, and appeared *"gloomy"*. They were noted to *"day-dream"* frequently and to be timid in the classroom. At age 13 they were noted to have *problems making friends* and there was some evidence they were *ignored by other children*. At 15 years they were noted *not to be "dare-devils"*. The only behaviour which appeared to change dramatically

between 13 and 15 for both boys and girls was *anxiety in class* where girls, particularly, showed a large effect at 13 for which there was little evidence at the later age.

In contrast to the excesses in these rather passive behaviours, neither girls nor boys destined to develop schizophrenia showed evidence of a tendency toward the more anti-social items or those suggesting over-activity and negative attitudes to others. Thus, there was no evidence of *disobedience, resentment of criticism, frequent discipline problems or restlessness during lessons.* There was some evidence at 15 of an association between *truanting* in girls; this may be considered not to be a manifestation of bad behaviour. In general, the pattern for these results was not that there was an association which just failed to reach significance, the majority of the odds ratios are scattered closely around unity, suggesting a truly negative result.

There was evidence that teachers considered that the children who would develop schizophrenia produced *poor or lazy work, not associated with poor concentration.* At 13, they were considered *unduly untidy*, although boys apparently lost this characteristic at the later age. Boys and girls were *poor at games and physical activities.* There were no cases who showed exceptional prowess at an out-of-school activity (Fisher exact test, 2-tailed, p=0.04) and both sexes showed an *excess of twitches and grimaces* at age 15.

Regarding differences between the observed associations for girls and boys, only cautious conclusions can be drawn regarding different odds ratios based on dividing-up such a small case group. In the majority of comparisons the confidence limits for girls overlapped those for boys and the differences between the odds ratios may have been due to chance. When testing formally for effect modification by gender, no interaction term was significant at the 5% level, although several approached this. Thus, at 13, girls appeared to avoid teachers attention, to be timid in class (although the effect was present for boys at 15) and to be ignored by other children, whereas

boys showed virtually no effects. At 15, girls appeared tired and washed-out and to avoid competition. Truanting was confined to girls at this age. In these items, the odds ratio adjusted for confounding by sex may not be a valid estimation of the true situation. There were other examples where an effect was more marked in girls than boys, but not confined to them, e.g. avoiding rough games at 15 years.

Table 4.11. Associations between adult onset schizophrenia and behaviour at age 13 years, as rated by class teachers. (OR = odds ratio)

Teachers' Comments on:-	Age 13 (1959)			
	Crude OR (95% c.i.)	OR boys	OR girls	Adj.* OR (95% ci)
Tired & Washed Out	3.4 (1-10.7) p=0.02	4.0	2.6	3.5 (1.01-11.7) p=0.02
Marked anxiety in class	3.8 (1.4-10.7)p=0.004	2.3	7.1 p<0.05	3.2 (1.2-9.2) p=0.01
Truants more than occasionally	Not available			
Ignored by other children	2.3 (0.5-8.2) p=0.2	1.1**	5.6 p=0.02**	2.3 (0.5-8.1) p=0.2
Shows marked changes in mood	0.8 (0.1-6.0) p=0.8	1.2	-	0.7 (0.04-5.5) p=0.8
Avoids rough games	1.8 (0.7-4.6) p=0.2	1.7	2.5	2.0 (0.7-5.1) p=0.1
Avoids teachers' attention	2.04 (0.7-5.4) p=0.2	1.0**	5.6 p=0.007**	2.2 (0.8-5.9) p=0.08
Not a dare-devil	Not available			
Avoids competition	3.4 (1.4-8.1) p=0.002	2.7 p=0.05	5.3 p=0.01	3.4 (1.4-7.8) p=0.002
Poor or lazy worker	2.2 (0.6-7.0) p=0.1	2.0	2.2	2.1 (0.6-6.5) p=0.2
Poor concentration	1.2 (0.4-3.8) p=0.8	1.2	1.1	1.2 (0.3-3.6) p=1.0
Very untidy	3.1 (1.1-8.3) p=0.01	2.8 p=0.05	2.5	2.7 (1.0-2.7) p=0.03
Work affected by environment (distractibility)	1.7 (0.4-6.2) p=0.3	2.4	-	1.7 (0.4-5.9) p=0.4
Exceptional at out-of-school activities	None. Fisher exact test 2-tailed p=0.04			
Poor ability at physical games	3.1 (1.2-7.3) p=0.005	2.5 p=0.01	4.1 p=0.04	2.9 (1.2-7.00) p=0.008
Appears gloomy	4.02 (1-14.3) p=0.02	3.9	4.3	4.0 (0.9-14.3) p=0.02
Timid in class and not quarrelsome	2.1 (0.7-5.9) p=0.1	0.7**	6.9 p=0.002**	2.31 (0.7-6.0) p=0.1
Resentful of criticism	0.8 (0.1-3.5) p=0.8	0.7	1.1	0.9 (0.1-3.8) p=0.9
Sometime or frequently disobedient	0.9 (0.3-2.5) p=0.9	1.1	0.5	0.9 (0.3-2.4) p=1.0
Discipline a problem	0.8 (0.1-3.3) p=0.7	0.5	1.4	0.7 (0.1-3.3) p=0.9
Restless in class	1.3 (0.6-3.0) p=0.5	1.3	1.1	1.2 (0.5-2.82) p=0.8
Frequently daydreams in class	2.9 (0.8-9.0) p=0.07	2.7	2.8	2.7 (0.8-8.5) p=0.1
Problems making friends	4.8 (1.4-15.0) p=0.002	3.1	8.8 p=0.001	4.6 (1.3-14.7) p=0.002

* = adjusted for sex. ** = interaction term for effect modification by sex, p=0.1

Table 4.12. Associations between adult onset schizophrenia and behaviour at age 15 years, as rated by teachers. (OR = odds ratio)

Teachers' Comments on:-	Age 15 (1961)			
	Crude OR (95% ci)	OR boys	OR girls	Adj.* OR (95% ci)
Tired & Washed Out	3.8 (1.2-11.0) p=0.02	2.3**	10.5 p=0.001**	4.3 (1.3-12.4) p=0.002
Marked anxiety in class	1.1 (0.4-2.5) p=0.9	1.5	0.7	1.1 (0.5-2.8) p=0.9
Truants more than occasionally	1.6 (0.7-3.5) p=0.3	0.9	3.6 p=0.05	1.51 (0.7-3.4) p=0.7
Avoids rough games	3.2 (1.3-7.7) p=0.01	2.5	7.9 p=0.004	3.7 (1.4-8.8) p=0.01
Avoids teachers' attention	0.9 (0.3-3.1) p=0.8	1.3	0.9	1.2 (0.3-3.6) p=0.8
Not a dare-devil	6.6 (1.5-2.4) p=0.001	9.0 p=0.001	5.7 p=0.07	7.6 (1.8-28) p<0.001
Avoids competition	3.0 (1.2-7.2) p=0.01	1.9**	8.9 p=0.002**	3.1 (1.2-7.4) p=0.006
Poor or lazy worker	3.4 (1.3-8.8) p=0.01	2.8 p=0.05	4.4 p=0.05	3.1 (1.2-8.1) p=0.008
Poor concentration	1.1 (3-3.5) p=0.8	1.0	1.2	1.0 (0.4-3.2) p=0.8
Very untidy	1.7 (0.4-5.9) p=0.4	1.1	3.8	1.4 (0.3-5.2) p=0.5
Appears gloomy	3.8 (1.1-11.9) p=0.03	4.2	3.1	3.8 (1.1-12.1) p=0.03
Timid in class and not quarrelsome	3.8 (1.4-9.7) p=0.01	3.6 p=0.02	5.5 p=0.01	4.2 (1.5-11.0) p=0.001
Resentful of criticism	2.0 (0.6-5.6) p=0.3	2.0	4.0	2.45 (0.8-7.0) p=0.1
Sometimes or frequently disobedient	1.1 (0.4-3.0) p=0.9	1.4	0.6	1.1 (0.4-3) p=1.0
Discipline a problem	1.1 (0.3-3.8) p=0.8	1.0	1.2	1.1 (0.3-3.8) p=0.8
Restless in class	0.9 (0.4-2.1) p=0.8	0.9	0.7	0.8 (0.3-2.0) p=0.8
Frequently daydreams in class	4.6 (1.6-12.3) p=0.002	4.13 p=0.03	5.6 p=0.07	4.5 (1.6-12.2) p=0.002
Noticeable twitches or grimaces	3.1 (0.9-9.6) p=0.03	2.5	3.7	2.8 (0.8-8.7) p=0.06
Thumb sucker	4.8 (0.8-22) p=0.02	8.2 p=0.001	-	5.05 (0.8-23) p=0.02

* = adjusted for sex. ** = interaction term for effect modification by sex, p=0.1

In most instances, given the low statistical power, there was remarkable similarity between the boys and girls, more so in the items related to school work and negative attitudes than those regarding social behaviour. This was the case for situations where an association appeared to exist, and those where the result was resoundingly negative i.e. odds ratios close to unity. It is interesting that there was convincing evidence of a greater effect for boys than girls in only one out of 25 items. Compared with their peers, this sample of girls who were to develop schizophrenia as adults appeared more abnormal than did the boys. However, this does not necessarily imply that, within this group, the behaviours of girls differed from the boys. The way the questions were phrased (more than average, average, less than average) meant that this question could not be addressed directly.

Analysis of continuous measures of behaviour

The multiple items of behavioural information at 13 and 15 years were simplified by the construction of continuous scores based upon a previous principal components analysis of the individual items which is archived at the NSHD and which was available for analysis (see Appendix). These continuous scores were analysed at both ages (Tables 4.13 & 4.14) in a manner similar to the IQ scores above.

At 13 the children's own ratings on the Pintner Aspects of Personality Rating were available as four scale, "emotional stability", "sociability", "negative attitudes to others" and "aggression" as detailed in the Appendix. The only significant predictor of later schizophrenia was the composite score of "sociability" (Table 4.13). Cases were least likely to be in the tertile containing the most sociable controls (OR 0.3, $p = 0.03$) and there was a significant trend ($\chi^2 = 4.0$, $p = 0.05$) over the tertiles; the less sociable a subject, the more likely they were to develop schizophrenia. Stratification by sex or social class made very little difference to the crude odds ratio, indicating

that this trend occurred in both boys and girls and in all socio-economic groups. There was no evidence that emotional stability or negative attitudes to others differentiated cases from controls. The trend for lack of aggression to be associated with cases was not significant, but was in keeping with the findings on anxiety.

At age 15 (Table 4.14) the scores derived from the teacher ratings gave further evidence of continuity with the results from two years previously. The scales were "anxious behaviour", "antisocial behaviour" and "habit behaviours" as described in the Appendix. There was a highly significant trend for increasingly anxious behaviour to predict later schizophrenia ($\chi^2 = 9.0$, $p = 0.003$). Many of the items from which this scale was derived were similar to those making-up the sociability scale which was a significant predictor at age 13. The was no clear pattern for aggressive behaviour at 15. Neither was there any evidence of an interaction with sex. The possible differences between girls and boys evident from the analysis of categorical data was lost when the items were all subsumed in to a continuous scale.

Table 4.13 Behavioural ratings Age 13. Low scores on sociability predicted cases.

AGE 13 EMOTIONAL STABILITY (HIGH = ABNORMAL)

Tertile	Cases	Controls	Odds ratio*	Adjusted OR**
lowest	9	1415	1	1
middle	7	1066	1.0	1.1 (0.36 - 3.3)
highest	9	1451	1.0	1.2 (0.4 - 3.3)
χ^2 test for trend* 0.00				
χ^2 test for trend** 0.1 p = 0.8				

AGE 13 - NEGATIVE ATTITUDES TO OTHERS (HIGH = NEGATIVE)

Tertile	Cases	Controls	Odds ratio*	Adjusted OR**
lowest	8	1308	1	1
middle	8	1244	1.1	1.0 (0.3 - 2.9)
highest	8	1389	0.9	1.1 (0.3 - 3.4)
χ^2 test for trend* 0.01				
χ^2 test for trend** 0.01, p = 0.9				

* Versus lowest tertile

** Adjusted for sex & social class

Table 4.13 cont.

AGE 13 - SOCIABILITY (HIGH = SOCIABLE)

Tertile	Cases	Controls	Odds ratio*	Adjusted OR**
lowest	14	1625	1	1
middle	6	882	0.8	0.8 (0.3 - 2.2)
highest	4	1424	0.3	0.3 (0.1 - 1.0)
χ^2 test for trend* 4.1, p = 0.04				
χ^2 test for trend** 4.0, p = 0.05				

* Versus lowest tertile
** Adjusted for sex & social class

AGE 13 - AGGRESSION (LOW = PEACEFUL)

Tertile	Cases	Controls	Odds ratio*	Adjusted OR**
lowest	11	1558	1	1
middle	6	980	0.9	0.8 (0.3 - 2.4)
highest	6	1432	0.6	0.5 (0.2 - 1.6)
χ^2 test for trend* 1.1, p = 0.3				
χ^2 test for trend** 1.5, p = 0.2				

* Versus lowest tertile
** Adjusted for sex & social class

Table 4.14. Teacher ratings of behaviour at 15. Anxious behaviour and habits predicted cases.

AGE 15 - ANXIOUS BEHAVIOUR (HIGH = ANXIOUS)

Tertile	Cases	Controls	Odds ratio*	Adjusted OR**
lowest	3	1337	1	1
middle	6	1394	1.9	2.0 (0.5 - 10.3)
highest	11	966	5.1	5.6 (1.4 - 24.6)
χ^2 test for trend* 8.1, p = 0.004				
χ^2 test for trend** 9.0, p = 0.003				

AGE 15 - ANTISOCIAL BEHAVIOUR (HIGH = ANTISOCIAL)

Tertile	Cases	Controls	Odds ratio*	Adjusted OR**
lowest	9	1478	1	1
middle	3	1011	0.5	0.5 (0.1 - 1.8)
highest	11	1213	1.5	1.3 (0.5 - 3.7)
χ^2 test for trend* 0.8, p = 0.4				
χ^2 test for trend** 0.7, p = 0.4				

AGE 15 - HABIT BEHAVIOURS

	Cases	Controls	Odds ratio*	Adjusted OR**
None	15	3081	1	1
One to three	6	786	1.6	1.5 (0.8 - 2.1)
four to six	1	13	15.8	17.1 (0.7 - 159)
χ^2 test for trend* 3.0, p = 0.08				
χ^2 test for trend** 2.9, p = 0.09				

* Versus lowest tertile
** Adjusted for sex & social class

The continuous data for habit behaviours at 15 showed a gross positively skew (79% of controls had a score of 0, range 0 - 6). For completeness, rather than because they had any bearing on this thesis, these data were re-coded into three categories, no habits, 1 to 3, and 4 to 6 habits reported. There was an excess of cases-to-be in both strata where habits were noticed, the case in the multiple habit stratum representing a highly improbable event (OR = 17.1, 95% c.i. 0.7 - 159, p=0.01) and the trend was significant at the 0.09 level.

These data were not analysed further in terms of the thesis due to the questionable validity of applying quantitative methods to qualitative data. For example, if a linear trend score had been calculated for the continuous measure of sociability then the resulting odds ratio, say 1.3 for the sake of argument, would have indicated that for each increase of one unit the risk (odds) of schizophrenia in the population would increase 1.3 fold. This is can be interpreted only if an increase in one unit has the same meaning right across the scale of measurement. The view was taken that this was an unsafe assumption but that dividing the distribution into thirds below average, average and above average did have some face validity, and the results were amenable to interpretation.

One further analysis is of relevance to the thesis in that it indicated that the linear trend in risk for IQ at 15 years was not attributable to behaviour. At 15, both anxiety (OR 1.3, $p < 0.001$) and the "IQ" score (OR 0.5, $p = 0.009$) were statistically independent predictors of schizophrenia in a logistic regression model, as usual accounting for confounding by sex and social class.

The possibility of a sub-group defined by several of the variables

The results so far have been in terms of univariate comparisons of *single* explanatory variables. The possibility of a multivariate sub-group, i.e. defined in terms of several variables together, has not been excluded. Given that the basis of multivariate analysis is the correlation or covariance between variables, a first step is the construction of a correlation matrix between variables of interest. A different pattern of correlations, or markedly different strengths of correlations, in cases and controls would indicate different associations between variables in the two groups and the possibility of sub-groups of cases with particular characteristics. Taken one stage further, there may be a sub-group of cases each of which has deviations from the norm, and a sub-group which has none.

Tables 4.15 a & b show the correlations for controls (Table 4.15a) and cases (Table 4.15b) between the motor developmental factor, age at talking, social anxiety scores at ages 13 and 15, and IQ at 15.

Table 4.15a Correlations between milestones, IQ and social anxiety (soc. anx.) in controls.

	Motor factor	Talking age	IQ at 15	Soc. anx. at 13	Soc. anx. at 15
Motor factor	1.0	0.15**	-0.01	-.0.02	0.06*
Talking age		1.0	-.0.01	-.0.03	-0.02
IQ at 15			1.0	-0.03	-0.08**
Soc. anx at 13				1.0	0.14**
Soc. Anx at 15					1.0

N of controls: 2950 2-tailed Signif: * - .01 ** - .001

Table 4.15b Correlations between milestones, IQ and social anxiety (soc. anx.) in cases

	Motor factor	Talking age	IQ at 15	Soc. anx. at 13	Soc. anx. at 15
Motor factor	1.0	-0.05	-0.51	-0.04	0.58
Age at talking		1.0	-0.07	-0.30	-0.22
IQ at 15		1.0	-0.45		0.10
Soc. anx at 13			1.0		0.38
Soc. anx at 15					1.0

N of cases: 15 No effects significant at 5%.

These correlations demonstrated a number of points. A general one, shown by the controls (Table 4.15a), was that with very large samples statistical and practical (or biological) significance are not the same. Even with the general hypothesis that positive or negative correlations might be expected, the statistically significant correlations were very small and likely to be unimportant; each variable explains virtually no variance in any other. In itself, that was an interesting finding provided that there was no bias due to the 37% of the controls having missing data (v.i.).

The correlations between the same variables in the cases (Table 4.15b) were generally larger which might have indicated a closer relationship between these variables in the cases than in the controls. However, the problem with small numbers was clear; there were only 15 cases (50%) who had values for each variable, a proportion not significantly different from controls with missing data ($p=0.2$). If the social anxiety at age 13 was omitted, then a sixteenth case was included but the results remained very similar. This resulting small case group makes the

statistical confidence plummet. None of the correlations was (statistically) significantly different from zero. With significant correlations in the controls so similar to zero there was no scope for safe interpretation of these results. Furthermore, with so few cases having complete data there was no possibility of examining the interesting question as to whether there would be a sub-group of cases with particularly tight correlations between the developmental variables which might be a reflection of a distinct, developmentally deviant sub-class of schizophrenia. Further multivariate analysis was not justified.

One more attempt was made to look simply for a deviant sub-group. It was doomed to failure due to small numbers of cases but it illustrates further points. A group of the risk set was defined which had all the characteristics of being in the latest thirds of talking and the motor factor, the lowest third of IQ at 15 and the most anxious third of the population at 15. The hypothesis was that schizophrenia would be more common in this multiply deviant group.

There were 60 such individuals, one of whom developed schizophrenia. The risk of schizophrenia in this long-term and highly deviant group (1/60; 1.7%) was raised compared with the risk in the cohort as a whole (30/4746; 0.6%). There were many individuals (1615) with missing data in one or more of the constituent items; 34% in the controls and 47% (n=14) in the cases. Some limits on the possible effects are given by including and excluding all those with missing data into the non-deviant groups. This gave risks of schizophrenia in the non-deviant population of 29/4686 (0.6%) and 15/3056 (0.5%), and unadjusted odds ratios of 2.7 (0.4, 20.3; p=0.8) and 3.4 (0.5, 25; p=0.7), respectively. The results were in line with the hypothesis but statistically very uncertain.

To put the finding further into perspective (and assuming that all cases of schizophrenia were identified and that the developmental deviance was closely related to causality) somewhere between 2% and 4.5% of all schizophrenia in the population may have been

"neurodevelopmental" as defined by the multiple deviance, with wide confidence limits. For the effect including all cases with missing data, the estimated population attributable fraction (PAF^2) was 2.1% with the upper 95% confidence bound being only 3.2%. The lower bound was "-5.7%", a value betraying the statistical imprecision which, without a prior hypothesis which allows the unlikely possibility to be dismissed, would suggest that being developmentally deviant *prevents* schizophrenia. The PAF excluding those with missing data was only 4.4% (-7.4, 6.0). The relative risks and odds ratios were modest, being little bigger than some of the individual components of the composite score (e.g. Table 4.6), and the population prevalence of the composite deviance was low (approximately 2%). Both these factors mean that the PAF was bound to be low. This line of analysis and its implications are considered further in the Discussion and again in Chapter 5.

Missing data and misclassification bias

The characteristics were examined of those survey members who had missing data for the 15 year educational tests. The proportions of cases (n=5, 16.7%) and controls (n=764, 16.2%) were almost identical, as were the proportions of boys and girls in the cases and controls (cases 2 girls missing, 40%; controls 366 girls missing, 47.9%). Parental social class of the cases with missing values showed no significant tendency to cluster (1 social class 1, 2 social class 2, 2 social class III-N), when compared with the social class distribution of all cases at 15; if anything, those who failed to do the tests came from more advantaged homes. The mean age at onset of those cases with missing values at 15 was similar to the remainder (23.4 years versus 24.4 years; 95% c.i. difference 6.1 years younger to 8.2 years older).

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[2] The proportion of schizophrenia in the population which might theoretically be prevented if this deviance were removed, assuming causality (Last, 1995).

As demonstrated in the previous section, missing data became a limiting factor when variables collected at different times were considered together. For individual variables which form the main subject of the thesis, missing data did not appear too great a problem; similar proportions of cases and controls had incomplete data for developmental milestones, IQ and social behaviour. However, there was no certainty that these data were missing at random in either group and imputation of missing values was not feasible.

The possibility that the diagnostic assessment from case records might have introduced bias was considered in two ways. First, the total number of cases was as predicted. If some true cases were missed then a similar number of false positives were included despite the two stage screen. This seems unlikely but remains possible. Second, cases in the two categories of diagnostic confidence (22 in the higher, 8 in the lower) were compared on a number of variables. They had very similar demographic characteristics, and the effects for IQ and milestones were virtually the same although statistical confidence was low due to the small numbers. For brevity, these results are not displayed. Misclassification in terms of DSM-III-R schizophrenia/schizo-affective disorder versus other diagnoses appeared an unlikely source of major bias.

Discussion

This investigation in an unselected, general population birth cohort indicated associations between a variety of childhood characteristics and adult onset schizophrenic illness. Despite no apparent social disadvantage at birth, age at walking was slightly, but significantly (statistically) delayed. Throughout childhood, shyness and awkwardness in social situations, and poor performance in tests of IQ predicted schizophrenia. In general the main arguments of the thesis were supported. It did not appear that risk of schizophrenia in the population was restricted to a particularly deviant sub-group as defined by these variables *individually*. An excess prevalence of categorical definitions of "abnormality" in terms of any single variable of interest in the children destined to develop schizophrenia gave only a partial view of the true situation for that population; there was no empirical justification for dividing the values of any single risk factor into normal or abnormal. The possibility of some latent, or multivariate developmental risk factor could not be excluded. Multivariate statistical analysis was precluded by the small sample but crude, exploratory analysis included only to be illustrative suggested that a putative, multiply deviant sub-group would account for only a very small proportion of cases of schizophrenia. If such a risk factor were to exist, the lack of any theoretical necessity to categorise it as present or absent is suggested by the main arguments of this thesis, and is discussed separately in Chapter 5. The present study was suitable only for the investigation of individual factors and it is this which is discussed below.

Methodological issues

As noted above, low statistical power is a methodological problem in studies of this kind, particularly regarding prediction of the future; complex models involving several predictors were simply not possible because there were so few cases who shared a large number of variables of interest; all had most, but too few had all. However, there were several strengths. The longitudinal nature of the data collection and the use of standardised cross-sectional information, such as the educational tests, avoided problems with biased recall. It is of interest to note that the mean age of teething, as recalled by mothers when the children were age 24 months, was slightly earlier for the case group, indicating that the other (later) milestone findings, which accord with current hypotheses, were unlikely to be the result of recall bias.

Selection of cases proceeded blind to information collected prior to age 16, and several independent sources of information were employed in order to identify the cases. In particular, use of the Mental Health Enquiry meant that survey members who had dropped-out of the NSHD follow-up could still be included as cases. There was only one permanent refusal of follow-up prior to age 16, so the risk set was representative of the immediate post-war generation, alive in the U.K.. Similar proportions of cases and controls had missing exposure data and cases with, and without missing data had onsets at similar ages.

The control group contained children who had, or later developed, severe illness other than schizophrenia, such as epilepsy and learning difficulties, which are known to be associated with later milestones and low IQ. This retained the population base of the controls, and was the most conservative approach in that it would have reduced associations between exposures and cases. As discussed below, van Os et al. (1997) have investigated developmental milestones in survey members who were identified as having chronic affective disorder during adult life. As children,

this group did show some of the same developmental characteristics as did children who later developed schizophrenia, though to a lesser degree. Retaining these in the risk set would again have been conservative, biasing effects towards the null. It was also correct; in our present state of knowledge, such individuals remain at risk of schizophrenia so should be included in the risk set as controls. However, this effect was probably very small, given the large size of the control group.

It was not feasible to divide the cases according to routine clinical characteristics owing to the small number and lack of fine-grained clinical detail. If differences in developmental associations do exist between possible sub-types of the adult clinical syndrome, it should be remembered that the estimates of associations will represent *underestimates* of the true effect in which ever sub-group is primarily involved. However, if this were the case, the findings of linear trends in associations for the total case group which was analysed would have been rather unlikely. This is discussed further in Chapter 5.

The findings

The cumulative risk of schizophrenia was within expected limits. Case identification was designed to ensure high specificity rather than sensitivity; with such a small number of cases, false positives would have been a serious problem. Nevertheless, the estimated risk of 0.63% by age 43 compares very favourably with the predicted risk of 0.61% by age 40 (Done et al., 1991). No statistically significant predictors of schizophrenia emerged from the measures of social class, although the trend appeared to be for higher social status at birth, a finding agreeing with the 1958 UK birth cohort (Done et al., 1991) and recent investigations in the 1966 North Finland birth cohort (Isohanni, 1997).

Within the early, motor milestones, later walking was the only statistically significant predictor of the cases, although there was a pattern for the cases to have reached all motor milestones later than the controls. Some reporting bias, leading to terminal digit preference, was evident in these data and will have lead to statistical imprecision through measurement error. Given that the control group included children with gross motor disabilities, the findings are likely to be real but subtle, particularly when account is taken for confounding by sex and social class. Later walking and other perturbations of motor development have been noted in schizophrenia in studies using a variety of designs (Robins, 1966; Walker & Lewine 1990; Fish et al., 1992; Ambelas, 1992).

As to the pathogenesis of these neurodevelopmental findings, there is as yet little direct evidence although they would fit with the neuropathological evidence of development going awry. They are unlikely to reflect primarily psychosocial effects. The later walking may reflect some abnormal developmental process continuing through the post-natal period into childhood, perhaps involving myelination of motor tracts. Normal myelination of hippocampal pathways extends into adolescence and this, or some perturbation, has been suggested as a mechanism for the delayed appearance of positive schizophrenic phenomena in adulthood (Benes, 1989; Murray, 1994). It is possible that delayed motor milestones were a manifestation of similar mechanisms, and even that the increased twitches and grimaces seen in adolescence represent their vestige.

The finding of poor educational performance predicting later schizophrenia reinforces evidence from several types of epidemiological study indicating a premorbid deficit in intelligence (Aylward et al., 1984). The first principal component of the educational test scores was analogous to the "G factor" of general intelligence consistently identified by previous workers (Crawford et al., 1992). Treated as a repeated measure, it differentiated cases from controls. Given the longitudinal nature of the data, with the same subjects involved at each age, and the population base of the study, these findings are compelling evidence in favour of pre-psychotic intelligence

deficits in schizophrenia occurring at least between 8 and 15 years, irrespective of sex or social class.

Regarding behavioural measures, children destined to be cases demonstrated remarkable continuity between 4 and 15 years, being characterised by an aloof, solitary habit with avoidance of social interaction. That this impression came from mothers, teachers and even the children themselves indicates a robust finding, reminiscent of the early reports of "asociality" and the "schizoid" premorbid personality (Kraepelin, 1896). There was no evidence of increased antisocial or aggressive behaviour, nor of conspicuous differences between girls and boys. Antisocial behaviour preceding schizophrenia, mainly in boys, has been reported in child guidance attendees (Robins, 1966) where findings may be difficult to generalise, and cohort studies where teachers' more open comments might have lead to antisocial conduct being particularly likely to be noted compared with shyness, the 1958 birth cohort study for instance (Done et al., 1994).

A model where the neurodevelopmental, educational and behavioural effects in childhood were manifestations of a single underlying process continuous with psychosis is parsimonious, but is not necessarily correct and was not supported by the analysis of IQ and behaviour, nor did milestone scores correlate well with IQ scores later in childhood (B Rodgers, personal communication). In the normal population there is no relationship between WAIS IQ scores and MMPI personality profiles (Lacks & Keefe, 1970; Bloom & Eaton 1975; Gaines et al., 1978), suggesting that personality and general intelligence, or "G", may be generated by largely independent neural systems. Thus, dysfunctional personality and low intelligence could act independently as risk factors for schizophrenia, presence of one and absence of the other will determine whether or not an individual crosses a threshold of risk where disorder becomes inevitable. It is only with a detailed and unbiased description of the period prior to psychosis

that these possibilities can be tested and extended to examine the notion of "robust" personality and high intelligence as *protective* factors.

The thesis: Developmental Risk for Schizophrenia - Evidence for a sub-group?

This study replicated previously reported associations between adult schizophrenia and certain characteristics of childhood development. In previous literature, analysis of categorical ratings of abnormality versus normality has tended to focus attention on the notion of a subgroup of cases who showed pre-psychotic deviance, with the assumption that other cases are normal. For example, low versus normal IQ, or late versus normal milestones. This approach ignores the wide range of scores found in the general population; just as for cerebral ventricle dimensions (Chapter 3) the majority of cases have "normal" values and the majority of "abnormal" subjects do not have schizophrenia. Categorical ratings are often artificial, applying arbitrary or poorly defined cut-off points. The present study was fortunate in that the availability of continuous measures of behaviour, personality and educational achievement enabled a more detailed assessment of the distribution of developmental risk.

The approach to examining frequency distributions for evidence of sub-groups of cases was simple, though nonetheless informative. There are sophisticated statistical techniques, such as admixture analysis (Harvey et al., 1991) for examining whether a frequency distribution is better described by two or more separate distributions but such techniques have low statistical power and would not have been of use here with only 30 cases. A population-based case-control study using routinely collected standard data regarding milestones and educational performance would be required. Such a study is feasible in countries where such data are available and were national case registers are kept, such as in Scandinavia.

Regarding the categorical approach to IQ as a risk factor, it was unhelpful and obscured a more parsimonious explanation applicable to the majority of the population. Data concerning milestones were interesting. They are precious in terms of this line of research but their characteristics, with peculiar recall bias, made them difficult to categorise and to analyse statistically. However, it was clear that the majority of cases had normal values; indeed, all cases were walking by two years. Thus, there appeared to be an effect of later milestones but its true nature was difficult to uncover particularly using a categorical definition.

The situation was different for the behavioural measures where, in some ways, the categorical measures gave more detail than did the composite, continuous scores; the possible interaction between certain behaviours and sex was an example. Once again though, it would be dangerous to conclude that only a minority of those children who developed schizophrenia had the "shy" behaviours. A minority crossed the threshold where their teachers marked the ratings as positive but those within the normal range may have been affected to a lesser degree.

The linear trend or continuous approach exploited the epidemiological basis to this investigation and allowed conclusions to be drawn concerning the population at risk of schizophrenia. This wasdone on the basis of defining which parts of that total population were responsible for the largest proportion of schizophrenia. Linear trends in the associations between schizophrenia and educational test scores gave a indication that the notion of a distinct, developmentally deviant sub-group who later suffer from schizophrenia *may* not portray the true situation, certainly in terms of aspects of the risk in the population. In terms of I.Q., the risk of schizophrenia appeared to be distributed through the population, such that, for any child, the lower the score in the educational tests the more likely they were to develop schizophrenia as adults; the risk of schizophrenia within the general population was not confined to a particular group. As schizophrenia is relatively rare, larger numbers (i.e. a larger population at risk), or a population-based case-control study, would

be required to examine the exact nature and distribution of this risk (e.g. is it quadratic or cubic as in Figure 2.1c or 2.1d?), but the simplest conclusion is that it is linear.

For the milestone data, terminal digital preference had a deleterious affect on this analysis and any conclusions have to be cautious; the thesis was neither supported nor refuted. For behaviour, the thesis was supported by the results of analysis of the continuous scales of "social anxiety" or social awkwardness". Despite the caveats regarding this particular analysis it did give direct evidence that categorical measures of behaviour may give an incomplete picture of the true nature of the distribution of the risk associated with the "schizoid" behaviour identified by Kraepelin; a dimensional view of this personality trait appeared to explain more about this relationship.

In conclusion, this investigation replicated a body of literature by demonstrating that children destined to develop schizophrenia in adult life can be differentiated from their peers across a variety of characteristics beginning with early milestones of motor and speech development. Indeed, this is the first general population sample in which all these individual developmental and childhood factors have been considered in the *same* individuals. Initial events in schizophrenia must occur early. The epidemiological base of the study indicated that incidence of schizophrenia was not confined to a sub-group of the population at risk in terms of childhood educational performance and "schizoid" behaviours, but appeared to arise increasingly frequently as IQ declined and scores on a scale of the latter increased. These conclusions require replication but, if true, provide a further, longitudinal dimension to the schizophrenia phenotype yet to be explained in terms of basic neurobiology.

As yet, there is little conclusive empirical evidence of a neuro-developmental *subtype* of schizophrenia, although the notion has driven understanding and investigation of the disorder and may yet prove to be correct. In this investigation it proved impossible to investigate whether there

was a sub-group of cases which were distinctly deviant compared with the majority in whom some effect was also evident; the number of subjects with complete data over time was too small to go beyond the most exploratory of correlational analyses which form the basis of multivariate investigations. Analyses such as multilevel modelling and neural network predictions would be ideal for exploiting this kind of longitudinal data in a larger sample but, even with imputation of missing values which with 50% missing data would have been a highly suspect tactic, was beyond the scope of this study. These lines of investigation should be done, though, with large samples probably from population-based case-control studies. The present sample was good for the univariate analyses but could not be pushed further. Such further longitudinal investigations, particularly if results can be pooled, will facilitate further exploration of the developmental antecedents of schizophrenia. The implications for a causal model of schizophrenia are considered in the general discussion in the next chapter. In this longitudinal setting and in terms of a variety of single developmental characteristics, the main argument of the thesis was supported.

Chapter Summary

Early deviance in physical, psychological and behavioural development has been linked with schizophrenia in adult life. The long time delay between these phenomena makes them problematic to study with precision and it is unclear what proportion of subjects with schizophrenia may be affected in this way. There is also a considerable overlap between measures of childhood development in cases and unaffected individuals. The argument in this thesis predicted that there would be a trend in the risk across the distributions, that there would not be clear evidence of a sub-type of the disorder, and that the data would support, or at least not rule out, the notion of a developmental effect of some kind in the majority of cases of schizophrenia, just as was shown for cerebral ventricle size in Chapter 3.

Childhood developmental milestones and IQ were ascertained prospectively in the British 1946 birth cohort study. Subjects have been followed to date and those 30 with adult onset DSM-III-R schizophrenia were identified up to age 43 years. Motor and cognitive development during childhood were shown to differentiate children destined to develop schizophrenic psychosis but there was no evidence that a sub-group of cases with low scores accounted for the effect. For I.Q. in particular, there was evidence of a linear trend in the association with risk for schizophrenia, as predicted by the arguments of the thesis. Ratings by mothers, teachers and the children themselves of social behaviour were also subjected to analysis as categorical and, where feasible, as continuous measures. The was some evidence that continuous measures described the risk for schizophrenia, but in terms of statistical analysis and the validity of the approach in this situation, this was less secure than for motor milestones and IQ.

Appendix to Chapter 4 - Details of the variables analysed as exposures.

Socio-economic status

Several indices of socio-economic status were available through childhood.

Birth. Occupational group of father.

Municipal characteristics of place of birth, i.e. city/urban/rural.

Population size (from 1961 census) of administrative area of birth.

Educational Achievement: Cognitive Test Scores

Results of cognitive tests were available for ages 8, 11 and 15 years. Both the tests and their development are described in detail by Pidgeon for the 8 and 11 year sets (Pidgeon, 1964) and those taken at 15 years (Pidgeon, 1968) Briefly, at age 8 four tests were given: a 60 item non-verbal picture test, a 35 item reading comprehension test (sentence completion), a 50 item word reading test, a 50 item vocabulary test (same words as above). At age 11 four tests yielded verbal, non-verbal, arithmetic, reading and vocabulary scores: an 80 item verbal and non-verbal test, a 50 item arithmetic test (problems and mechanical sums), a 50 item word reading test, a 50 item vocabulary test (same two tests as at age 8). At age 15 years three tests gave similar scores to those at 11: the group ability test - a 65 item verbal and non-verbal test, the Watts-Vernon reading test (Also given at age 26), a 47 item mathematics test.

Thus, there were non-verbal and verbal scores available at all three ages, mathematics/arithmetic at 11 and 15, vocabulary at 8 and 11 and reading at 8, 11, 15 and 26 years. In the NSHD archive these scores have been "normalised" to give mean 100, standard deviation 15.

Early milestones

During the health visitor interview at age 24 to 26 months, mothers were asked to recall the age to the nearest whole month that the survey member had:

sat alone

stood alone

walked alone

talked - saying more than names of familiars

cut the first tooth.

Health visitors noted if they found evidence that the survey member had not reached any of these milestones.

Social and behavioural characteristics

The earliest data on social behaviour came from maternal reports of play preferences at age 4 and 6 years. Mothers were asked whether the child usually played alone, with siblings, with other children, or in other (unspecified) circumstances.

At age 13 the children themselves completed the Pintner Aspects of Personality Inventory (Pintner et al., 1937; Pintner & Forlano, 1938). Four continuous measures were available for analysis. These were based on a previous principal components analysis of the three scales derived from this test (Rodgers, 1990 a&b) and comprised:-

Emotional stability (range 0-13, mean 3.9) - based on items such as "I often feel sad for no reason at all' and "I worry about the little mistakes I make".

Sociability (range 0-8, mean 4.8) - e.g. "I make friends easily", "I feel at home at parties".

Negative attitudes to others (range 0-11, mean 3.7) - e.g. "I find that very few people can be trusted" "I often get blamed for things I didn't do".

Aggressive behaviour (range 0-7, mean 3.7) - e.g. "I feel I have a right to fight for what I want", "I sometimes feel like hitting people".

At ages 15, questionnaires were completed by survey members' teachers who were asked to make global assessments in areas such as sensitive/highly strung, aggressive, shy. More specific ratings of certain behaviours, habits and attitudes (e.g. to school work) were also made. Children were assessed on a three point scale, (less than class mates, same as classmates, more than classmates). This information was available in both a raw and in a processed form. The latter was based upon principal components analysis, which gave three scales comprising continuous data with approximately normal distributions for the first two, the third being positively skewed:

Anxious behaviour (range 13-32, mean 20.5) - e.g. "timid child", "frightened of rough games", "always 'washed out'" .

Antisocial behaviour (range 13-35, mean 18.9) - e.g. "poor or lazy worker", "frequently disobedient", "frequently evades the truth".

Habit behaviours (range 0-6, median and mode zero) - e.g. "nail-biter", "frequently twitches or grimaces".

These scales are precursors of the Rutter A & B scales.

Chapter 5

General Discussion

Introduction

The results from the investigations in the cross-sectional survey and the longitudinal study have been considered in the context of the literature relevant to each topic in Chapters 3 and 4, respectively. Here the results and implications are treated in a more general way with reference to the main arguments in the thesis.

Empirical support for the arguments in the thesis

Summary of findings from this investigation

To recap briefly, the main hypotheses in the CT analysis of brain structure related to cerebral ventricle volumes, and a resolution of the debate in the literature regarding the overlap of dimensions between cases of schizophrenia and controls. Explanations predicated on one-to-one, specific causal mechanisms provided a poor explanation of the data. Freed from this explanation based upon mid-nineteenth century views, an alternative using a model of risk factors contributing to, or associated with, the notion of causal constellations (see Chapter 1), resulted in a more adequate explanation of the data. The most likely situation was a linear association between increasing dimensions and increasing risk.

That these ventricle dimensions were probably far from being a single or strong causal factor was suggested by the majority of the variance in whether or not a subject was a case or control remaining unexplained. In terms of the dimensions measured, risk for schizophrenia was not confined to a sub-group of the study subjects. Had the study been truly population-based, one

could infer that this risk was distributed throughout the population in a particular way; the larger the dimensions, the greater was the risk.

Subsidiary hypotheses related to whether there would be greater extra-cerebral CSF volumes in schizophrenia, and whether these volumes would also have a linear relationship with schizophrenia, rather than a threshold effect. These hypotheses were not supported and results were equivocal. The imaging technique used was not really adequate for the accurate estimation of this variable; random measurement error may have obscured any true effects. These hypotheses would better have been examined by MRI.

The absence of predicted associations between possible causal variables (family history and obstetric complications) and cerebral ventricle size was interesting. This may lend support to the view expanded later that there might be aetiological heterogeneity (many possible causal constellations) but that this leads to a more homogeneous mechanism, betrayed by I.Q., personality (see Chapter 4) and cerebral ventricle dimensions, prior to a heterogeneous clinical syndrome of schizophrenia. Once again, this requires a study with more refined instruments, such as MRI, and a sample where all variables are available on all subjects.

In the longitudinal analysis of the British 1946 birth cohort there were similar findings concerning the risk of adult schizophrenia associated with childhood I.Q. This was a robust variable probably affected least by information bias compared with the other variables used here to examine the main arguments of the thesis Lower I.Q. in the group of children who would develop schizophrenia was confirmed. It appeared not to be due to a sub-group of children but to an effect on the majority, or even all. This study was population-based, so one can go on to infer that the risk of schizophrenia, as betrayed by childhood I.Q. scores, is distributed throughout the population. Once again, there must be many other factors, or a few very strong effects, involved

in a causal constellation as the proportion of variance in case-control status explained by IQ was minuscule. Given the population base, an alternative approach to this point would have been to have estimated the positive predictive value of a logistic regression model containing I.Q. at any one age or, better still, I.Q. at each age, together with confounders such as sex and social class. This approach was not presented because so few cases had complete data for all variables (see Chapter 2 for further justification). Suffice it to say here that a model with I.Q., sex and social class predicts over 99% of subjects correctly by assuming all are controls; not a single case could be predicted.

The examination of behaviour and early milestones provided some support for the notion that these characteristics, too, might not be either "normal" or "abnormal" in children who develop schizophrenia. They may vary in degree in schizophrenia, with the possibility of a large proportion of cases being affected, but with only a minority of them crossing some arbitrary threshold into abnormality as defined in terms of the whole population. Once again, we are far from the true causal constellation when considering only these variables, or even all the variables together, as the proportion of variance explained (or true cases predicted) was tiny.

As discussed in detail in Chapters 3 and 4, there were a variety of methodological drawbacks to both these investigations. However, they did provide some support for the notion that causes in schizophrenia (or characteristics betraying causes, i.e. risk indicators) should not all be formulated in terms of single, factors which are both sufficient and necessary. In terms of the possibilities discussed in Chapter 2 and set out in Figure 2.1, it was, as predicted, the situation illustrated by Fig. 2.1b that best described the data. It is acknowledged that the true situation may not be exactly a straight line relationship. The investigations did not provide support for the notion that the particular factors included were strongly influential in determining whether or not someone has, or will develop the clinical syndrome of schizophrenia. This was not the purpose of the

thesis; schizophrenia is not a disorder of I.Q. or of ventricle dimensions, but they appear to be clues as to the components of a causal constellation(s) and as to how such components might act.

Support from elsewhere

Direct and strong support for the conclusions regarding I.Q. has been provided by G. Lewis and colleagues (Lewis et al., 1996) who have studied 50,000 young men conscripted at age 18 years into the Swedish army during the period 1969/70. Conscription involved over 95% of the male population. Young men are given extensive psychological tests and personality ratings prior to entry into the army. Using record linkage to the Swedish Hospital Discharge Register, 195 (0.4%) of this cohort were identified as having been discharged from a psychiatric hospital between the ages of 18 and 25 with an ICD 8 diagnosis of schizophrenia.

Lewis and colleagues replicated the finding of a linear trend in the association between IQ score at age 18 and subsequent risk of schizophrenia. Their large sample enabled them to investigate the nature of that trend to a greater degree than was possible in the British cohort reported here. Rather than just three divisions, they were able to calculate the trend in risk across nine divisions of the population distribution of I.Q. scores. This relationship was remarkably linear. There was a deviation towards higher risk than would have been predicted by a linear equation at the very lowest tail of IQ, but this category was a "catch all" of scores lower than a certain level, something which may have accounted for this effect.

It is of interest, but not of direct relevance to this thesis, that Lewis et al., (1996) also replicated the finding of an asocial, schizoid personality, assessed at 18 years of age, as being a predictor of schizophrenia. Subjects with few friends at conscription, who preferred to socialise in small groups, who had no steady girlfriend and felt more sensitive than other people were more than

thirty times more likely to develop schizophrenia than were men with none of these characteristics. That this was not merely a result of a minority of men in the prodrome of their illness was indicted by the persistence of this effect when the analysis was restricted to cases who developed schizophrenia after the age of 20 years. Unfortunately, there were no continuous data available regarding behavioural ratings, so the existence of linear trends in risk for schizophrenia as defined by behaviour could not be replicated.

Further work on the Camberwell Collaborative Psychosis Study has provided evidence of support for the thesis within behavioural measures and school performance, taken as a proxy for IQ. Unfortunately, behavioural data were not collected from the CT controls collected by Lewis (1993) which have been used in Chapter 3. Cannon and colleagues (Cannon et al., 1997) have collected a second, independent control sample from people attending the Accident and Emergency Department at Kings College Hospital, the general hospital serving the area in which the majority of the cases lived. In this study, information from a modified version (Foerster et al., 1991) of the Premorbid Social Adjustment Scale (Cannon-Spoor et al., 1982) based upon interviews of mothers was subjected to principal components analysis. This yielded two, continuous behavioural scales. One concerned sociability the other school performance, each one available for two phases, childhood and adolescence. Obstetric and family history data were also collected as in the cases. With some 100 cases and 100 controls this study had greater statistical resolution than the analyses in the NSHD (Chapter 4) but relied on retrospective accounts in a sample which was not truly population based.

Once again, there was no evidence of a sub-group effect. Cannon et al., (1997) demonstrated clear trends in the association between risk of schizophrenia and both sociability and school performance. These appeared best described by linear, straight line equations, rather than anything more complex, just as Lewis et al., (1996) indicated. Interestingly, Cannon's findings

were not specific to schizophrenia but occurred also in affective psychosis, although to a lesser degree. The issue of specificity is discussed later in this chapter.

Thus, there is corroborative and largely independent evidence in favour of the main arguments of this thesis, as applied to behaviour and I.Q. These two characteristics may be considered as contributing weakly to some constellation of predisposing causes, (more simply conceived as early or remote contributions to a causal constellation), completed later by later or more proximal events which might precipitate the schizophrenia syndrome. The weakness of this contribution to the total causal constellation is indicated by the small proportion of variance explained. Alternatively, these factors might be considered as the earliest manifestations of the syndrome itself. The problems and current futility of debating this question have been outlined in Chapter 1. If the presence or absence of these, or any other factors is associated with the probability of disease occurring then they are most succinctly considered as "risk factors". Moreover, if there is less schizophrenia in situations when they are removed or lessened then they can usefully be considered as part of a cause. A key issue is how schizophrenia is defined. Here, it is as a cross-sectional syndrome, as described in Chapter 1.

However, to most eyes it would seem as though I.Q. and behaviour are shaped, or caused, by other events; the results of brain structure and function, and their determinants, in particular. Is there any independent evidence to support the notion that risk of schizophrenia associated with these factors is also distributed throughout the population, as suggested by the CT analysis in Chapter 3? This would be in contrast to the situation where discrete abnormalities act as necessary and sufficient causes which are absent from the majority of the population.

Attempts to define a sub-group of schizophrenia on the basis of the presence or absence of "enlarged" cerebral ventricles (the corollary of the main argument of the thesis) proved

unsuccessful (Harvey et al., 1990b; Daniels, 1991; Vita et al., 1996), indicating a population shift compared with controls as would be predicted by the current thesis. Indeed, the first two of these studies, which failed to show a sub-group, influenced the original development of the ideas in this thesis.

Support for the arguments in this thesis comes from the studies of a series monozygotic twins discordant for schizophrenia which have been carried out by Torrey, Weinberger and colleagues (Torrey, 1994). It was noted in Chapter 3 that the cerebral ventricle size, and hippocampal and general cortical volume of the group of affected twins was not greatly different from the group of control, unaffected twins. However, when each affected twin was compared with their unaffected co-twin there was a systematic difference, indicating consistent pathology in those with schizophrenia (Suddath et al., 1990). This systematic difference has now been demonstrated for a wide range of physiological (Weinberger et al., 1992), personality and cognitive tests in these twins (Torrey, 1994). This indicates a widespread effect in schizophrenia despite absolute values of continuously distributed variables showing widespread overlap in cases and controls.

There are two caveats to this evidence from twins. Firstly, the evidence from each of several domains is not independent of that from another since it is all based upon the same relatively small sample. Secondly, schizophrenia in twins may not be the same entity as that in general population singletons. However, the evidence provides another view of the arguments within this thesis and is remarkably consistent with its conclusions.

As noted in Chapter 3 and supported by this MZ twin work, one implication of the finding that an effect on cerebral ventricle size may be widespread within schizophrenia is that a majority of affected individuals show a small but consistent effect. Only a minority of all those affected

cross a threshold into "abnormality", defined in terms of the population. Such an effect on gross cerebral structure may be a manifestation of an underlying, widespread microscopic effect (Stevens, 1982). To date, there is little evidence to judge whether or not the microscopic changes found in the disorder are widespread throughout the brain. The work is technically demanding and researchers must necessarily concentrate on specific areas. There is pathological evidence to suggest that the whole brain is different in terms of size (Bruton et al., 1990), although certain areas may be more, or primarily affected, such as the prefrontal cortex (Akbarian et al., 1993 a&b) or the hippocampal and parahippocampal areas (Kovelman & Schiebel, 1984; Jacob & Beckman, 1986).

Some consider (e.g. Weinberger, 1995) that the most valid neuropathological data have been those provided by Akbarian and colleagues. They used a particular histological stain (nicotinamide-adenine dinucleotide phosphate-diaphorase) to identify specific sub-populations of neurones in the frontal and temporal lobes. In schizophrenia, these neurones were fewer in number compared with controls and their distribution, skewed to the deeper layers of the cortex, suggested a developmental problem during the period of cell migration (Akbarian et al., 1993 a&b). That this occurs in (at least) two large regions of the brain suggests the kind of general underlying lesion posited by Andreasen (1994; see Chapter 1) but its distribution within the group of subjects with schizophrenia was not clear. Akbarian and colleagues seemed to suggest a prevalence of around a third of cases. However, their definition of presence or absence of the abnormality was obscure, their numbers were small, their statistics not aimed at testing for linear trends and, as seems a reasonable, but perhaps an unfair guess, they were expecting a sub-group effect. As outlined in Chapters 1 and 3, the appealing nineteenth century idea of subgroups with necessary and sufficient causal factors is hard to relinquish; the causal thinking does not always seem to evolve at the same pace as the technology.

An intriguing example of a linear trend in risk of schizophrenia and a structural characteristic determined during early development (late first/early second trimester) has been provided by Fananas colleagues (Fananas et al., 1996). On the basis of the excess of categorical, minor physical abnormalities reported in schizophrenia (Green et al., 1987), considered to be "fossilised" evidence of problems in ectodermal development (such as those identified in the brain by Akbarian et al; v.s.), Fananas tested the hypothesis that dermatoglyphic markers would be similarly abnormal in the disorder. Blind to case or control status, they measured the total a-b finger ridge count in the palm prints of a group of 38 subjects with schizophrenia and in a control sample of 69 subjects. Not only were mean values of this continuous measure lower in cases than in controls, but there was also a linear trend in the risk associated with the ridge count. Here, too, one could conclude that the greater the ridge count for anyone in the population, the greater the risk of schizophrenia. This effect was assumed to be an indicator of aberrant brain development which would occur at the same time as the ridges are formed; the second trimester. The associated conclusion based upon the case group alone is that there was evidence of a population shift in the cases with the likelihood of a widespread effect, rather than one relevant only to a minority.

A further example from this area comes from a study by Lane (1996) who took the findings of discrete minor physical abnormalities further by developing a metric scale giving a continuous measure, just as in the A-V ridge count study of Fananas and colleagues (v.s.). Measures of the mid- and lower facial region accurately distinguished 174 subjects (not all incident cases so the effects *may* relate to chronicity, not the development of schizophrenia) with schizophrenia from 80 matched controls, as would have been predicted from the literature on minor physical anomalies. When the distributions of the continuous measures were compared in the cases and controls there appeared to be a population shift in the cases (John Waddington - personal

communication), supporting the present thesis and suggesting, once again, the notion of a widespread, early effect.

If the relevant influences (genetic or environmental) on the developing fetus are involved with the cause of schizophrenia then they are either rare in the population at risk and have a strong effect, or they are ubiquitous but require the presence of a separate factor(s), acting either at the time or over long period. In a research study, this latter situation would be manifest as a statistical interaction or effect modification - if one could only identify the relevant factors and study them. This argument still assumes the presence of factors other than those measured on continuous scores (be they I.Q., behaviour or ridge count). These manifest factors may appear to be categorical but their effects may not be. For instance, a knotted umbilical cord either happens or it doesn't but the degree of secondary fetal hypoxia may have an infinite range of values.

Two characteristics which might be candidates for alternative, rare constituents of causal constellations have been shown to have the dose-response relationship with schizophrenia that the thesis would propose. This strengthens the argument that they may be involved in causation of schizophrenia, although it is unlikely that they often occur as parts of the same causal constellation. One, cannabis consumption, is a proximal factor exerting any effect close to the onset of the schizophrenia syndrome. The other, fetal exposure to maternal famine during the first trimester *in utero,* must either exert or begin to exert its effect very early in life. The cannabis association described by Andreason et al., (1986) comes from the same Swedish conscript cohort used by Lewis et al., (1996) and concerns reported cannabis consumption in men by age 18 years and subsequent schizophrenia. The famine association comes from the studies of the Dutch Hunger Winter by E Susser and colleagues (Susser & Lin, 1992; Susser et al., 1996). The dose-response relationship strengthens the argument that these factors are

involved in causation but indicates that other factors must also be involved. They are not necessary and specific causes, as required by the Koch-Henle postulates.

Consideration of genetics has been conspicuous by its absence in this discussion of risks and causes. Mindful of the danger of straying too far from the territory and variables of the previous chapters, a number of points can be made to suggest that genetic risk, too, may be better understood as a continuous risk factor.

It is as tempting to consider genetic risk for schizophrenia (or for anything else) in terms of an all-or-nothing phenomenon as it is to consider environmental events or personal characteristics in this way. The phrase, "the gene for schizophrenia" is one that may be used to lampoon molecular genetic research, probably because the idea of a necessary and sufficient genetic contribution to schizophrenia is so obviously an *inappropriate* explanation of the results of family studies of the disorder (Gottesman & Shields, 1982). The notion akin to Koch's postulates suggested by classical genetics, where autosomal dominant and recessive disorders are "one gene, one disorder", had to be relinquished decades ago. Addition of "penetrance", the phenotypic expression of a genotype which may vary from zero to 100%, to causal models has also proved an unsatisfactory explanation of data from genetic epidemiological studies of schizophrenia (Asherson et al., 1995). However, it is unfair to be too dismissive of a monogenetic theory of schizophrenia in this context given that, as originally advanced (Slater, 1958), the gene was considered a necessary but not a sufficient cause.

In this line of research the relative genetic effect in groups is expressed either by a simple proportion affected (often of relatives) or a weighted proportion depending on the ages of the individuals (Slater & Cowie, 1971). These proportions, or morbid risks, are continuous variables but in contrast to the variables used in Chapters 3 & 4 to examine the thesis, they do

not relate in any direct way to the individuals in the group who are either affected or unaffected. Use of survival analytical techniques stresses the individual relatives but these subjects must still be assembled into groups according to characteristics of the probands. An attempt has been made by Sham and colleagues (Verdoux, et al., 1996) to construct a system of weights which does result in a measure of an individual's genetic risk but that risk is still conditional upon other members of the family and the comparison groups. Grouping probands themselves according to a categorical assessment of presence or absence of disorder in their families has given rise to another categorical aetiological classification of schizophrenia into familial and sporadic forms (Murray et al., 1985; Lewis et al., 1987; reviewed by Roy & Crowe, 1994) which has already been discussed in Chapter 3. Right or wrong, this classification has certainly had great heuristic value (Murray & Jones, 1996).

There are several mechanisms, however, by which addition of a continuous dimension to genetic risk might apply to individuals. Firstly, the DNA comprising genes can be considered active only when translated into RNA, thence to proteins which are ultimately responsible for any genetic effect. Jones and Murray (1991) have pointed out that genetic risk for schizophrenia might usefully be considered in terms of which proteins are responsible, so illuminating both mechanisms and putative causes of the disorder. Under complex control, protein synthesis which is responsible for phenotypic expression of genes can be viewed most usefully not only as a continuous effect with variable amounts of the gene product available, but also one which may vary over the life course. Jones and Murray (1991) suggested some likely candidates but the paucity of knowledge limits this "candidate gene" or "candidate protein" approach (Harrison & Geddes, 1996).

Current attention in schizophrenia genetics has moved away from the realms of reductionist, one gene, one disorder models (OGOD models) towards the ideas of general, behavioural genetics and

the notion of *quantitative trait loci (QTL).* In contrast to the OGOD approach, QTL involves the search for multiple genes, each one of which is neither necessary nor sufficient for the development of a trait (Plomin et al., 1994), and has a *small* effect. The combination of the effects of these multiple genes (i.e. the proteins for which they code) is distributed throughout the population in a manner which may reasonably be described by a normal distribution. For characteristics such as cognitive ability and behaviour there may then be a linear, or other continuous relationship between genotype and phenotype. A crucial difference between OGOD and QTL is that the protein products in the latter are not necessarily abnormal in any way although they may be; it is their combination which makes certain phenotypes more likely. The notion of multiple genes with small effects which underlies QTL is reminiscent of, and entirely in accord with the notion of causal constellations with multiple causes or risks having variable individual effects; it is the sum total which determines the outcome.

One further example of a continuous genetic risk comes from the recently described phenomenon of trinucleotide repeats. These seem to underlie a range of genetic disorders including autosomal dominant ones such as Huntington's disease, myotonic dystrophy and spinocerebellar ataxias, and X-linked recessive disorders such some sub-types of fragile X, and the Kennedy syndrome (Morrison, 1996). Rather than the loss of DNA or a small change in the nucleotide sequence, trinucleotide repeat diseases occur when a portion of DNA consisting of a triplet of more than one type of nucleotide (e.g. GAA or CAG) becomes unstable and the number of copies increases. The number of copies determines some of the characteristics of these syndromes, particularly "anticipation" where the severity increases and age at onset falls in succeeding generations, a phenomenon which has been suggested to occur in schizophrenia and bipolar affective disorder (O'Donovan et al., 1995). Interestingly, there does appear to be a threshold phenomenon *and* a dose-response relationship in operation. Below 35 repeats the DNA is stable and there is no abnormal phenotype. Above 35, the number of repeats can expand catastrophically into hundreds

or even thousands, with the severity and age at onset of the disrder increasing and decreasing, respectively, in a dose-response manner.

This leaves a problem, though, for schizophrenia when it is formulated as a cross-sectional clinical syndrome which may be either present or absent according to current operational criteria[3]. Even if a relationship between the syndrome and spectrum personality disorders is accepted, and family studies suggest it should be, there remains the problem of the relative rarity of paranoid, schizoid and schizotypal personality disorders. If a less specific or concentrated combination of genes were required for these disorders then they might be expected to be considerably more common than schizophrenia, which they seem not to be (Weissman, 1993). Risk factors for these disorders are not well established. The application of the present methods and risk factors would be an interesting line of research, if only to investigate specificity of the general model and of the risk factors, themselves.

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[3] It is acknowledged that it is somewhat illogical to construct a thesis supporting the idea of continuous risks over categorical ones, thereby accommodating overlap between affected and unaffected subjects, whilst constraining the outcome to be a categorical one (i.e. RDC or DSM schizophrenia). The defence is that outcome had to be constant in order to formulate clear hypotheses in the light of current concepts of schizophrenia and the existing literature pertaining to the chosen risk factors. Allowing the outcome/disease to be dimensional would be a logical next step, although the theoretical underpinning to such an approach is not yet well established. Dimensions within a categorical definition of schizophrenia are accepted (e.g. symptom dimensions, outcome dimensions) but the disease definition itself is yet to be formulated in this way with any success. van Os (1994) provides an authoritative review.

Could the investigation strategy have resulted in the wrong conclusions?

It is possible that the methods used in this thesis may have resulted in the wrong conclusions. Specific, methodological reasons are discussed first, followed by of a more profound problem.

Chance was dealt with by the statistical tests and confidence limits in the empirical sections. The probability of a type one statistical error was greatly diminished by the similarity of the findings from the two independent studies reported here, and from the studies cited above as providing external support.

There are two further possibilities under the rubric of information biases which may have lead to the trends reported. The first is a systematic measurement bias. For instance, if CT measures were over-estimated for the cases, but not the controls, there would have appeared to have been a population shift. This can be discounted due to the blindness built into the CT scan image analysis and the prospective nature of the NSHD longitudinal study. It is a particular problem, though, for studies where blindness is not possible such as the maternal recall of childhood personality traits where "effort after meaning" may be operating, or the non-blind assessment of minor physical anomalies. Not only would it lead to differences in mean scores but, if widespread, would result in a population shift.

The second possibility concerns random measurement error and the problem of being able to divide the case and control groups into three divisions as part of the strategy of examining the nature of a the trend in risk. This limit had to be used owing to the limited numbers of subjects. Had there been a true threshold effect as shown in Figure 2.1a, and that threshold had been in the middle of the population (control) distribution, a spurious linear trend would have been apparent. There is no external evidence or *a priori* hypothesis to suggest that this would have been the case.

More likely is the possibility of a threshold somewhere within one of the outer thirds of the distribution. If there were random measurement error, such that a proportion of subjects was wrongly assigned to each third, then any true threshold effect would have been diluted and may have appeared as a trend. This is unlikely for two reasons. Firstly, when the variables (e.g. cerebral ventricle volume or I.Q.) were modelled as continuous variables a regression term for a non-linear trend might have been expected to fit the data better than a linear trend. The major statistical power constraints (Rose, 1992) in this regard have been acknowledged. Secondly, Lewis et al. (1996) had sufficient cases in the study of Swedish conscripts to divide up the population into nine bands and still found strong evidence of a linear trend.

By far the biggest problem with the thesis is betrayed by the foregoing, rather manic defence of it. The ideas presented have been supported by a wide assortment of evidence but none has been falsified. One or two hypotheses have not been supported, such as those relating to the presence of larger extra-cerebral CSF spaces in schizophrenia. These negative results were likely due to methodological weaknesses, particularly the problems of random measurement error compounding limited statistical power. These hypotheses were by no means excluded; absence of evidence is not evidence of absence.

In terms of current, Popperian views summarised Chapter 1, the thesis has not advanced knowledge one iota. Hypotheses regarding continuous risk have been defined, and refined a little, but they await falsification before we can be *certain* that we must look elsewhere. It is cheating to claim that the double negative of disproving null hypotheses represents such Popperian proof. In terms of Carnap's views, the arguments become more and more likely to be correct as further evidence accumulates. Nevertheless, we must remain *uncertain* until we can be sure they are incorrect.

Thus, the problem becomes more acute the more evidence is collated in favour of the current hypotheses. The IQ evidence from the Swedish conscripts (Lewis et al., 1996) is a good example. It would have been something of a relief had this larger data-set and more fine-grained analysis shown evidence of a sharply defined threshold. The idea of a continuous risk could have been discounted, subject to the chance of a type I error, leading to the certain knowledge that the truth rests elsewhere. At least the arguments and hypotheses remain amenable to testing, in the areas studied in this thesis and in others.

Implications for schizophrenia and its causes

If they do represent the truth, the main implication of the findings is that a model of necessary and sufficient causes of schizophrenia, as suggested by Koch's postulates (Chapter 1), is not supported, at least in terms of the individual risk factors discussed. The trends in the associations between these risk factors and the occurrence of schizophrenia implies that they might better be considered in terms of constellations of factors (Rothman, 1976) which can be judged as being causal or not, according to criteria for chronic disease (Hill, 1965; Susser, 1973). This has many implications.

In terms of the population at risk of schizophrenia, it may not be helpful to think in terms of normal versus abnormal when considering many of the factors that may be part of any causal constellation, or indicators of risk. Where such factors are distributed throughout the population, such that each person has some of the factor (the precise distribution is not important), everyone in the population may be considered at risk for the disorder. That risk is quantifiable in terms of the relevant factor. It has been shown that the risk increases linearly across the distribution for

some factors. It should be borne in mind that the absolute risk for any individual likely remains fairly low as schizophrenia itself is not common; it is relative risks that have been considered. As discussed in Chapters 3 and 4 in terms of the relevant factors, risk for schizophrenia is not, therefore, combined to a sub-group of the population with the remainder exempt. The majority of the disorder arises within the majority of the population at medium risk.

The "risk" model explains the overlap in distributions between affected and unaffected, as demonstrated in Chapter 3; this is a puzzle only in a model of single, specific causes. The corollary to this is that any causal effect may be widespread within those who develop schizophrenia despite the possibility that the effect may be quite small. For example, it has been argued that the larger mean volumes of cerebral ventricles, or lower childhood I.Q. in case groups compared with controls may be a reflection of a large proportion, or even the majority of the former group manifesting a small causal effect. Consequently, only a minority of them are statistically abnormal, and concentration on that group in analytic strategies obscures this widespread effect. Indeed, quite a large, widespread effect may be manifest by this strategy. This is demonstrated in Figure 5.1.

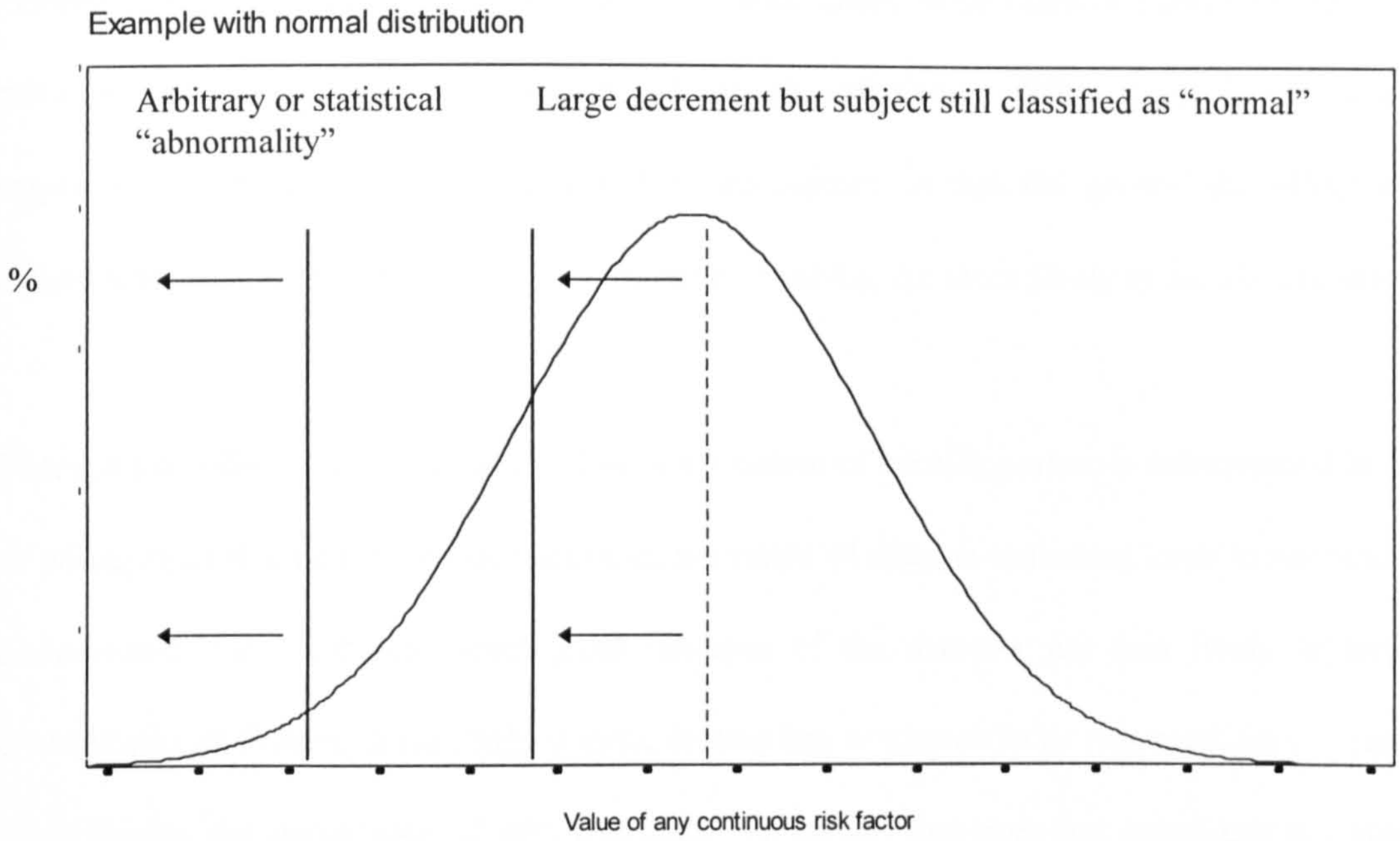

Figure 5.1 A large decrement within a normal distribution can leave a subject classified as "normal"

Figure 5.1 demonstrates the point within a normal distribution. A subject well within the normal range might suffer a major decrement but not be detected by a strategy or instrument designed to detect only statistical abnormality. This is a nice example of an epidemiological method applied to groups, having implications for *individuals.* The shift in the group, mean value reflects a widespread effect in those individuals making values from one end of the distribution steadily less common than those from the other.

Note, though, that if characteristics such as IQ and ventricle size are all risk indicators, having no direct causal role, then this notion of widespread effects may not be so clear. There may be a number of discrete, antecedent causal events that precipitate a limited number, or even a single chain of events leading to psychosis. Homogeneity of developmental or cerebral characteristics does not preclude antecedent, aetiological heterogeneity. Such antecedents may not inevitably lead to psychosis, particularly as their own effects may not be as categorical as they may at first seem. An example is the possibility that was suggested above of a range of fetal hypoxia resulting from an obstetric event which may be either observed or not. This situation begins to resemble

"Hume's Problem" described in Chapter 1. Without falsification there is always the danger of a missing measurement or variable undermining an inference. What does follow from the arguments of the thesis, assuming that they are correct, is that the greater the effect of any antecedent cause as measured by the intervening variables, the more likely is the disease outcome.

There is a corollary for the illness itself once the notion of specific causes is relinquished in favour of widespread risk factors; aetiological classifications of disease outcomes have to become more dimensional, too. Discrete aetiological subtypes of the disorder are less likely in terms of continuous risk factors, particularly if those factors can be shown to be risk modifiers - removing them lessens the occurrence of schizophrenia. However, that does not invalidate the study of singular cases or groups (Murray et al., 1985). A causal constellation model incorporates the possibility of some cases of disease being caused by high doses of a risk factor making others unnecessary, or rare constituent factors having a major effect. Studies of these particular situations will illuminate causation and may have implications for the majority of the illness.

According to the criteria for causal inference discussed in Chapter 1, the dose-response relationship adds to the evidence that the risk factors are part of, or linked closely to causal constellations. For the two main classes of risk factors examined, brain structure and childhood developmental characteristics, this causal constellation must be assumed to operate over a long period of time. There is either a latent period over which individual effects are cumulative, or a number of factors, including brain and personality maturation, have to be in place before the whole causal constellation can exert any effect - something that takes time to occur (Rothman, 1981). This maturation could itself be termed a risk factor.

The causal criterion of specificity for the factors considered in the thesis is not so clearly satisfied. In Chapter 3 it was shown that the association of ventricle size, particularly of third ventricle, was

not confined to schizophrenia being found also for affective psychosis. This is in accord with four recent, large meta-analyses of studies of ventricle dimensions and sulcal prominence in subjects with affective disorders (Elkis et al., 1995). Findings were qualitatively similar to schizophrenia although slightly lesser in degree.

Regarding specificity of the childhood developmental findings in the NSHD, van Os and colleagues (1997) attempted to replicated the findings in Chapter 4 for affective disorder. The case definition did not use a standard operational classification system due to inadequate data. However, it benefited from contemporary assessments of mood in childhood, the PSE symptom score at age 36 years and a similar symptom check list at age 43 years in order to define depressive "caseness". Subjects with childhood onset depression and those subjects with chronic depression in adult life showed similar, but less severe developmental and I.Q. effects than those with schizophrenia, although the childhood behavioural effects were dissimilar.

The investigation by Cannon et al., (1997) using the alternative controls in the Camberwell Collaborative Psychosis Study that showed similar childhood behavioural trends in schizophrenia as those in the NSHD, also showed those in affective disorder, predominately bipolar illness. Again, they were similar in nature but of lower magnitude.

Finally, the Swedish Conscript Study of G Lewis and colleagues (Lewis et al., 1996) also included 192 men with ICD 8 psychotic diagnoses other than schizophrenia. As might be expected from the foregoing, there was a trend in the association between lower IQ and these diagnoses, but smaller than for schizophrenia. Interestingly, the trend appeared not to be linear, indicating the possibility of different mechanisms, and a distinction between these conditions and schizophrenia based on something other than the cross-sectional phenotype at presentation.

Rothman (1976) is dismissive of the specificity criterion as being informative regarding causality. In the case of the examples above there may be several reasons why lack of specificity is no reason to doubt the importance of the particular risk factors. The usual line of defence in physical disease epidemiology comes from the smoking and lung cancer association. Merely because smoking is associated with many diseases other than lung cancer does not mean that it is not causal in that condition, or in any other. The term "smoking" is very crude given that smoke contains thousands of chemicals, and the same chemical may have many effects. Just so in the examples in this thesis. Later milestones is a very crude term that may be the result of a variety of quite different mechanisms, and any one mechanism may have a variety of outcomes. Conversely, there may be implications for the disease outcomes themselves; schizophrenia and affective psychosis may be aetiologically linked, and few would doubt that they are imperfect, working definitions at present. The same particular factors may be single parts of a number of different causal constellations. That they may not be single sufficient and necessary causes means that a reconsideration of aetiology in schizophrenia or psychosis might require changes in their classification. It was noted in Chapter 3 that the third ventricle dimensions might more properly be risk factors for *psychosis*, with other factors determining other aspects of the clinical syndrome. This possibility could be investigated empirically.

Might there still be aetiological subgroups in schizophrenia?

The answer is yes. The results in the thesis have not excluded the possibility of subgroups, although it has been argued that they are likely to account for only a small proportion of the disorder. The existence of rare, secondary schizophrenias (Lewis 1995) has been acknowledged, and there is a strong argument that schizophrenia is an umbrella term that will one day be split completely into a range of secondary disorders. This thesis argues against this only in degree. There will be only a limited number of causal constellations and mechanisms that account for the

majority, though not necessarily all, of the disorder. The ubiquitous factors in terms of which the position of the thesis was argued are unlikely to be directly causal. If they are involved at all in any causal constellation(s) they may in fact be indicating "mechanisms". Once one has given-up the notion of single specific causes, the distinction between a mechanism and a constituent of a constellation of causes becomes indistinct.

Thus, there may be a number of distinct factors that could be said to contribute to causation. These might be interchangeable with each other within a constellation of other factors, or each may contribute uniquely to several constellations, most of which would include ubiquitous characteristics such as I.Q. or ventricle dimensions. It has been explained above that these ubiquitous characteristics might be affected to a considerable degree in a majority of affected subjects but remain within a statistically normal range. The distinct aetiological factors might include a variety of early events such as exposure to pre- or post natal viral infections, prenatal famine or perinatal hypoxia, or they might include more proximal events such as psychosocial stress or drug abuse. However, given that there *may* be innumerable other factors involved it may also be premature to assume the existence of aetiological subgroups. Also, there is no convincing evidence of any resulting clinical syndrome being distinct.

Another possibility regarding subgroups is raised by the notion of causal constellations. There may be distinct groups of causes. This would effectively give rise to aetiological heterogeneity, even if some factors were common to one or more constellations. Statistically, this is the possibility of multivariate subgroups. Merely because it has not been possible to demonstrate subgroups amongst the univariate, single factor analyses the existence of subgroups defined in several dimensions has not been excluded. Exclusion of statistical interaction between two or several variables is a first step which has been attempted here. Neither the data nor the hypotheses were sufficient to attempt to exclude subgroups defined by a large number of

variables. In Chapter 4, exploration of the idea of a stronger correlation between some factors in the schizophrenia group than in the controls, indirect evidence of a possible constellation of factors occurring more commonly in the cases, had to be abandoned because so few subjects had complete data. Full exploration of this important question would require a large sample, complete data and very strong hypotheses but is possible. It is a logical next step.

There is still the question as to whether some subjects with schizophrenia tend to manifest multiple impairments with the rest having the same as in the general population. As explained, attempts in Chapter 4 to examine co-existence of factors over time broke down due to small numbers. The attempts were included only to be illustrative. They indicated that the more tightly the relevant combination is defined, the smaller becomes the proportion of schizophrenia, or any other disorder, which may be attributed to the combination. The models become less useful in this numerical sense, although it is acknowledged that the cause of "functional" schizophrenia in even one individual would be a useful piece of knowledge.

This difficulty with investigating a sub-group may be considered as another example of the main argument of the thesis. The individual factors by which abnormality may be defined do not themselves seem to have threshold effects. Why then should their combination? There is no need even to postulate this. In terms of multivariate statistics, there may exist some latent variable(s) defined in terms of a combination of several measured ones; a developmental deviance factor, for example. Would such a latent variable behave as a continuous risk factor as in Figure 2 b or c, or would it have a threshold effect? Would high doses of it (severe, multiple impairments) be associated with schizophrenia, and lower levels with absence of the disorder? Perhaps there would be a clear separation of values in the population into two groups, normal and deviant. Would cases below the threshold, or in the "normal" group, have some other aetiological variant of schizophrenia?

A suitable sample would allow these questions to be answered, but not the samples used here. My prediction, given the results from the individual variables, would be that there would be no threshold; all cases would be affected to some degree. The opposite is quite feasible. This is a key question for the argument in this thesis which, by investigating individual factors alone, might be said merely to have defined this question more clearly. The circumstances necessary to answer it are considered below in the section on future work.

Implications for the prevention of schizophrenia

High risk and population approaches

The major goal of understanding the nature of causal factors is that they may then be removed and the incidence of the particular disease reduced. Indeed, this notion was introduced in Chapter 1 as a simple definition of a cause and, in the guises of the dose-response relationship and the results of experiment, accounts for two of Hill's criteria for judging causality. However, if the conclusion that risk factors in schizophrenia may operate continuously is accepted, two approaches to removing those risks are possible; the high risk and the population approach. The broadest discussion and clearest description of these strategies have been provided by Rose (1992).

The notion of the high risk approach is very common in medicine. Arbitrarily defined hypertension, hypercholesterolaemia, alcoholism or obesity are all treated in an effort to reduce illnesses for which they are risk factors; indeed, the approach suggests the widely accepted idea that these deviations from normal are themselves illnesses. This approach can be of great benefit to those at high risk but, as mentioned above, the majority of illness may result from the majority of the population who are at lower risk; there are just so many more of them. The relationship between risk and numbers of individuals at risk is demonstrated in Figure 5.2, adapted from Rose

(1992). Thus, the majority of disorder cannot be prevented by a high risk approach *unless* there is a threshold in the relationship between disease and risk, as shown in Figure 2.1a, and unless values above the threshold account for a large proportion of the disease. This thesis provides no support for this relationship in terms of the individual risk factors examined, the most likely relationship being that suggested in Figure 2.1b and extended in Figure 5.2.

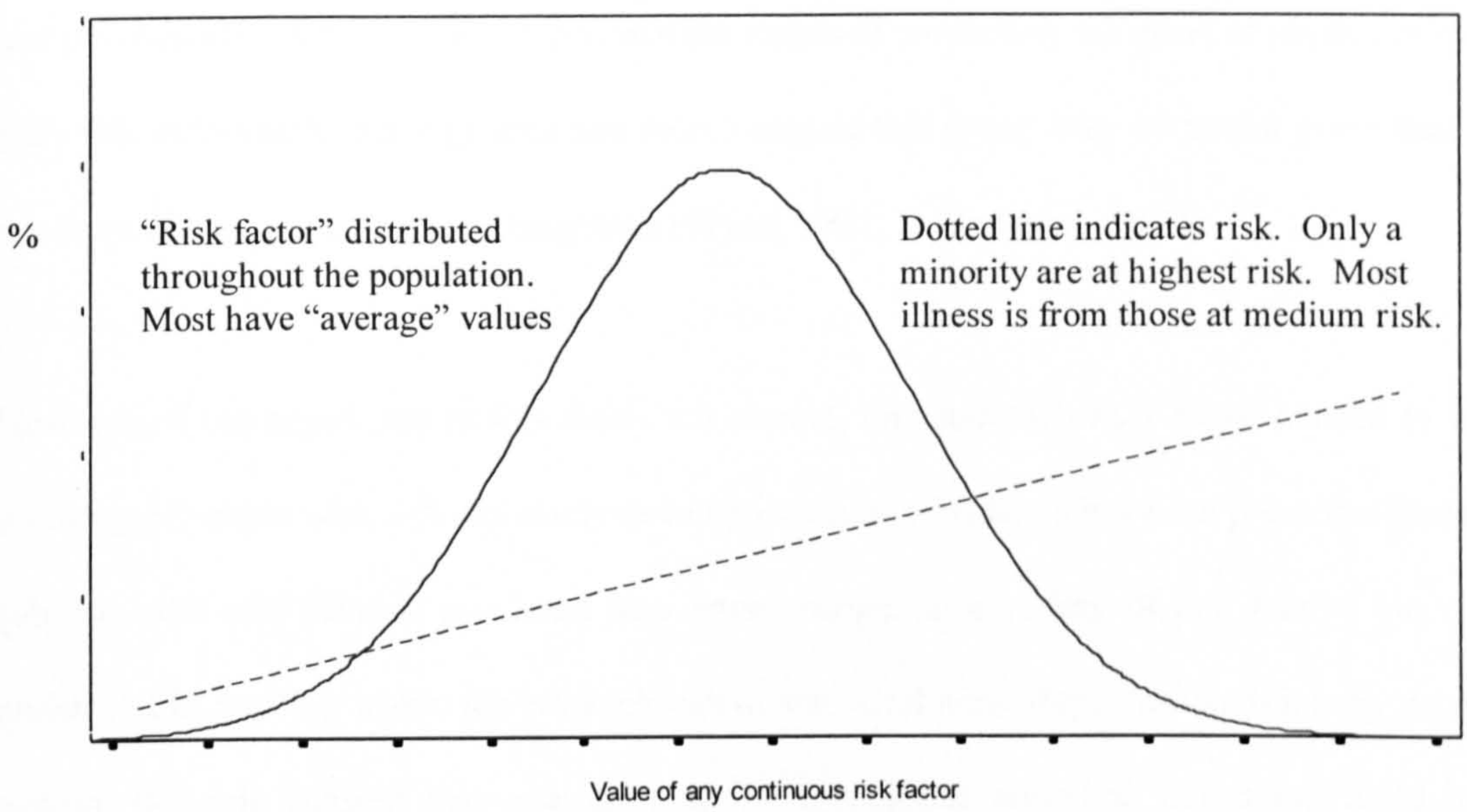

Figure 5.2 Relationship between risk and numbers at risk.

The relationship between risk and numbers of subjects within the population indicates that a strategy that concentrates on the whole population and achieves a small reduction in risk in every individual (or most of them) will bring about a greater reduction in disease than will a strategy that concentrates on only those at high risk. Rose (1992) presents data suggesting that for stroke a high risk approach to hypertension, eliminating it all together by treatment might, at best hope to prevent 10% of the disorder whereas a 10% reduction in blood pressure throughout the population by a decrease in salt intake would eliminate a quarter of all strokes (Law et al., 1991). The first is

virtually impossible to envisage, the latter quite possible to achieve. For many illnesses Rose argues for a combined approach.

This raises the exciting possibility of population approaches to the prevention of schizophrenia and other disorders which may be associated with the same continuous risk factors. It may one day be possible to identify a high risk developmental profile in children which has useful predictive value, perhaps with the addition of genetic information to longitudinal social, clinical and psychometric data. We do not yet have the means of preventing the onset of psychosis even in high risk individuals, but vigilance and monitoring of this group may be useful given that early interventions appear to improve prognosis (Wyatt, 1991; Loebel et al., 1992).

However, if the arguments in this thesis are correct, this approach may be of benefit to only a minority of people who will ultimately develop psychosis; evidence has been presented that many subjects who will develop psychosis may have changes in a variety of risk factors but remain undetectable, nestling within the broad church of statistical normality. Although it is by no means certain, the data suggest that a broader set of approaches aimed at improving child health, development (physical and psychological), and achievement at school might have a far greater impact and, if it were effective at all, may *prevent* schizophrenia rather that allow its early treatment. This does not mean that, say, I.Q. score and ventricle size have a direct causal link to schizophrenia and psychosis, but it does assume that a broad approach would modify those other risks or constituents of the cause which are indicated by these characteristics.

The prevention paradox and lack of specificity

High risk approaches require high positive predictive values because the interventions usually have considerable implications for the individuals concerned; side effects from a life time of drugs, for example. On the other hand, benefits to the individuals are high, in terms of avoiding

illness. For example, this would mean that a trial of neuroleptic treatment in adolescents deemed to be at high risk from psychosis would have to involve only individuals at virtually 100% risk of illness, such that the high risk of side effects of currently available drugs might be an acceptable cost. This is not possible as yet and, with current predictive models it is difficult to see how a trial to establish the efficacy of such an intervention might achieve scientific or ethical support.

Population approaches generally employ less draconian interventions, such as the minor reduction in salt intake mentioned above. However, each individual in the majority at medium or low risk, from which the majority of illness arises is unlikely to become ill. Unlike the few at high risk, they have to make a sacrifice, albeit small, for little individual benefit despite it having considerable implications for the whole population. This is Rose's "Prevention Paradox". With more common diseases, the paradox usually lessens as it does when the inconvenience of the intervention is small; mass fluoridation of water to prevent dental caries is a good example of a preventative population intervention with a low degree of paradox.

For the population approaches to lowering the risk factors for psychosis discussed here, this paradox is minimal or even non-existent, at least given our current understanding of the mechanisms determining growth and development. Improved antenatal care, nutrition, other socio-economic conditions and education will benefit all, even if the savings in terms of reduction in schizophrenia are small (or even non-existent!).

A similar defence is also available against those who argue that the increasingly apparent lack of specificity of the associations between child developmental milestones, school achievement, cerebral ventricle size and schizophrenia (or even psychosis) lessens their importance. On the contrary; if some hypothetical mass intervention might reduce the incidence not only of schizophrenia and other psychosis, but also of conduct disorder, depression, and perhaps have

widespread benefits through improved health, wealth and intelligence, then all to the good. Lack of specificity is a benefit so long as the associations between risk and outcome have the causal properties of dose-response and reversibility described by Hill (1965).

One might speculate on whether such a natural experiment has occurred with the ecological association between general improvements in health which have taken place over the current century and the evidence for a concurrent reduction in the incidence of schizophrenia (Der et al., 1990), at least in those populations where the improvements have been found (Castle et al., 1991). In populations where they have not, such as early generation migrant groups, particularly those from the Caribbean, the incidence is higher (Harrison et al., 1988 & 1997; Wesseley et al., 1991; King et al., 1994; Selten & Sibjen, 1994; van Os et al., 1995). Further speculation might include the notion that it is not the absolute level of health in these migrant groups which is important, but the level relative to the host population, a discrepancy which would tend to decline over the generations. Such a situation would mirror the curious but robust finding in general epidemiology that it is the range of inequality in a population which determines its health rather than the absolute values of social deprivation or wealth (Davey-Smith, 1996). Such speculation echoes Rose's view (Rose, 1989) that:

> *".....psychiatric epidemiology and psychiatric preventive action merge into social research and social policy. The two cannot exist apart".*

Future work

All that has been presented here must be replicated in population-based samples of incident cases of schizophrenia. If the results are not replicated and can be falsified, then the thesis quite rightly falls on its face. If replicated, the specificity of the findings must be tested to their limits. As

noted above, it would be exciting to me if they were not specific. There is a particular need for investigation of biological characteristics, such as cerebral structure and genetic diathesis, within an epidemiological design. As ever, large samples are ideal; indeed, they are vital in the context of examining further the true nature of the association between risk and disease, to tease apart the possibilities presented in Figure 2.1 which would underpin a population approach to prevention, and to examine multivariate risk.

As replication proceeds so must the formulation of possible causal models of schizophrenia, other psychoses and, possibly, a wide range of mental illnesses. Just as happened in the nineteenth century with the acceptance of Koch's postulates, this will allow new views on disease entities themselves. The boundaries of cross-sectional clinical syndromes may be redrawn in the light of multifactorial causal models, whilst the definition of longitudinal phenotypes may provide evidence of common mechanisms and antecedent causes in several disorders. Both the high risk and population approaches to prevention will be facilitated by this strategy, and research into the causes of schizophrenia may rejoin the fold of chronic disease epidemiology. The clarion call of Geoffrey Rose for psychiatric epidemiology to look to the social and political sciences is well taken but, if our understanding is to progress further than mere "risk factor-ology", then it must also look through the other end of the telescope towards basic science and the understanding of pathogenesis.

Chapter Summary

The empirical findings in Chapters 3 and 4 were reviewed. The individual continuous risk factors studied appeared not to have any thresholds in their association with risk for schizophrenia; risk was demonstrated throughout their ranges. Just as there was no requirement to split the risk factors into present or absent categories, there may have been no reason to split schizophrenia into subtypes on an aetiological basis. It was acknowledged that there were methodological shortcomings to the present study but several studies providing supportive evidence were reviewed.

The results were interpreted as suggesting that causal models including continuous risk factors, should at least be considered for schizophrenia and other psychoses. Such factors may best be considered within constellations of many factors. Those that can be modified are of greatest interest. This view has implications for possible strategies for prevention which might usefully include the population approach as well as the high-risk approach.

In the light of the methodological shortcomings, particularly the inability of the thesis to investigate multivariate risk, suggestions were made for future work.

Chapter 6

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Cerebral ventricle dimensions as risk factors for schizophrenia and affective psychosis: an epidemiological approach to analysis

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SYNOPSIS A case–control study was undertaken of volumetric computerized tomographic scan measures in 216 consecutive admissions for functional psychosis and 67 healthy community controls. Odds ratio analysis demonstrated significant linear trends in the association between increasing lateral and third ventricle volumes, and both RDC schizophrenia ($N = 121$) and schizoaffective disorder ($N = 41$); cases were consistently associated with larger volumes than controls. There was an association between larger third, but not lateral, ventricle size in affective psychoses ($N = 54$). These associations were statistically independent of intracranial volume, sex, social class and ethnicity, factors which were significantly associated with ventricular measures in the controls. There was no evidence of a threshold corresponding to the notion of normal *versus* enlarged ventricles.

Within the schizophrenia group, there were no large or significant associations between ventricle dimensions and age at onset, duration of illness or pre-morbid social functioning. Neither obstetric complications nor a family history of schizophrenia or other psychiatric illness was associated with large ventricles in these cases.

INTRODUCTION

The existence of structural brain changes in schizophrenia, particularly large lateral cerebral ventricles, is widely accepted. However, some fundamental questions remain unanswered. Some reviews (Lewis, 1990; van Horn & McManus, 1992) have highlighted the paradoxical trend in more recent X-ray computerized tomography (CT) studies to find smaller and smaller differences between controls and schizophrenia cases. In addition, the definition of what constitutes pathology has been a problem for all neuroimaging research, particularly when the size of structures has been the focus of attention; the distributions of structural dimensions in comparison groups have consistently shown considerable overlap (Smith & Iacono, 1986; Smith *et al.* 1988; Harvey *et al.* 1990*a*; Birley, 1992). These phenomena remain largely unexplained, despite the focus of structural imaging research having moved to magnetic resonance imaging (MRI). Nevertheless, the accessibility of CT scanning results in a current advantage in terms of the feasibility of scanning large, representative samples.

The search for clinical and aetiological correlates of ventricular enlargement has provided contradictory results (Goetz & van Kammen, 1986; Shelton & Weinberger, 1986; Lewis, 1990 for review). Just as in the case of ventricle size, this may be due to selection bias, or small samples and Type II errors, particularly where the true effect sizes are small; few studies include more than 100 patients with schizophrenia (Takahashi *et al.* 1981; Gross *et al.* 1982; Owens *et al.* 1985; Andreasen *et al.* 1990*a*; Sacchetti *et al.* 1992). Previous authors (Raz *et al.* 1988; Smith *et al.* 1988) have drawn attention to bias that may arise from using medically screened subjects as controls, rather than healthy community volunteers; even the latter may be biased towards a high prevalence of psychiatric disorder

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(Halbreich *et al.* 1989; Shtasel *et al.* 1991). The ethnic constitution of samples is rarely reported. Available results have not suggested significant group differences in ventricle size (Weinberger *et al.* 1979; Pearlson *et al.* 1985) but there are documented ethnic and gender differences in head size (Khang-Cheng *et al.* 1980; Andreasen *et al.* 1990*a*) that merit further examination in normal people. In addition, Lewis (1990) has noted that, although many CT studies have examined the rôle of factors such as obstetric complications (OCs), few have had sufficient statistical power to make their results readily interpretable.

This case–control study was designed to explore the relationship between the functional psychoses and intra- and extra-cerebral cerebrospinal fluid (CSF) spaces using high resolution CT imaging, and employing a sample size and analytical methods sufficient to assess both schizophrenic and affective psychoses, free from confounding by sociodemographic characteristics. We sought to avoid the unsolved problem of how to define abnormality (Smith & Iacono, 1986), specifically what constitutes ventricular enlargement, by using the distribution of ventricular size in the controls as the basic unit of measurement. Affected cases can then be examined in terms of where they lie within this distribution, the relative positions of cases and controls being expressed as an odds ratio, which can be equated with risk, allowing the direct estimation of both effect sizes and the contribution of sampling error. The results can be compared directly across studies, and can be contrasted with multiple regression or analysis of variance, the techniques that are usually employed in this area (Zatz *et al.* 1982; Zatz & Jernigan, 1983; Pfefferbaum *et al.* 1988; Harvey *et al.* 1990*b*; Jernigan *et al.* 1990). Volume and area measures of the lateral ventricle (LV) correlate well (Penn *et al.* 1978; Zatz & Jernigan, 1983; Reveley, 1985), but there have been suggestions that volumetric measures might give better discrimination between cases and healthy controls (Gado *et al.* 1982; Raz *et al.* 1987). By using a unifying scale (the population distribution), this analytical approach allows the degree of similarity between results based on areas and volumes to be quantified.

We predicted that there would be an association between both large ventricle volume and extra-cerebral CSF spaces and schizophrenia, but not affective psychosis. We wished to quantify the size of this association, in order to be able to evaluate its aetiological rôle, and to establish whether ventricle size should be considered a continuous risk factor for schizophrenia, or whether increased risk of the disorder is confined to a subgroup of individuals with particularly large ventricles. We predicted that the former model was more likely given the considerable overlap in ventricular dimensions found in schizophrenia and comparison groups. Furthermore, we wished to examine the association between brain structure and possible aetiological factors, namely, obstetric complications and family history of psychosis, hypothesizing that each would be associated with large ventricles in schizophrenia. Finally, we wished to attempt to replicate associations in schizophrenia between large ventricle size and both young age at onset and abnormal pre-morbid social adjustment, and to examine the effect of chronicity.

METHOD

Selection of cases and controls

Cases of functional psychosis were drawn from two cross-sectional samples of consecutive hospital admissions, the Camberwell Collaborative Psychosis Study (Jones *et al.* 1993*a*) and a sample drawn from an adjacent health district (Harvey *et al.* 1990*a*). Sampling procedures were virtually identical for both studies. All hospital admissions aged 16 to 60 years were screened and recruited if delusions, hallucinations or formal thought disorder, as defined in the Research Diagnostic Criteria (RDC) of Spitzer *et al.* (1978), were present without evidence of focal neurological disease, or other organic cause such as epilepsy, RDC drug use disorder or alcoholism. Initial diagnostic assessment comprised the Present State Examination (Wing *et al.* 1974) and case note review. Cases were included in this study if, in addition to their psychotic symptoms, they fulfilled the RDC for schizophrenia, schizo-affective disorder, bipolar I disorder, manic disorder or major depression and, having given informed consent, underwent CT scanning.

Controls were unpaid volunteers actively recruited from three main sources: a Salvation

Army training college in South London, a local Job Centre and the employees of the Institute of Psychiatry and associated hospitals. Inclusion criteria for volunteers were the same as for the patients, other than that controls were excluded if there was evidence, from a semi-structured interview, of the RDC disorders mentioned above, including alcoholism.

This is the first analysis of CT scans from the complete admissions and control series; technical CT analyses concerning a sub-group of the cases have been reported elsewhere (Harvey *et al.* 1990*a*, *b*), as have data concerning premorbid behaviour (Foerster *et al.* 1991*a*, *b*), socioeconomic status (Jones *et al.* 1993*a*) and life events (Bebbington *et al.* 1993).

Socio-demographic and clinical assessments

Socio-economic status at birth or during early childhood was assessed for both cases and controls using the Registrar General's classification of paternal occupation. This was recoded into three groups; social class 1 and 2, class 3 or class 4 and 5. Ethnicity was classified as either white European or other ethnic group. An estimation of verbal intelligence was derived from the New Adult Reading Test (Nelson & O'Connell, 1978; Nelson, 1982) except in 74 cases where the verbal sub-set of the WAIS (Wechsler, 1955, 1958, 1975) was employed to yield a comparable measure (Crawford *et al.* 1992).

In the cases only, a rater who was blind to proband characteristics including diagnosis, interviewed mothers with regard to the family history (as defined by the Family History RDC, Andreasen *et al.* 1977) and obstetric history. Obstetric complications (OCs) were rated as absent or definitely present according to the scale of Lewis *et al.* (1989), except that rapid labour was no longer classified as an OC; this scale has been validated by O'Callaghan *et al.* (1990). Further details of these assessments are published elsewhere (Foerster *et al.* 1991*a*, *b*). Age at onset was defined as the age at which the proband first saw any medical practitioner for psychotic symptoms, and pre-morbid social function was rated according to the scale of Phillips (1953).

CT scanning

Axial CT scans were performed on one Siemens 9800 scanner between 1987 and 1992. Pilot, lateral skull X-ray ensured standard initial orientation in the transverse plane. Slices 1 cm thick, parallel to the floor of the anterior fossa and ascending to the vertex were analysed at an independent viewing console (IVC). Three raters, blind to other information on the subject, each rated an equal proportion of both case and control scans; inter-rater reliability was high ($r > 0{\cdot}9$ for each measure). Intracranial area was measured on each slice by summing all pixels in the range 0 to 100 Hounsfield units (HU; Hounsfield, 1973) within the skull. A border just peripheral to the brain/cerebrospinal fluid (CSF) boundary of the third and lateral ventricles was traced manually and the IVC required to sum pixels from 0 to 25 HU within this area. Areas of the lateral and third ventricles were measured in all slices where they appeared, and a LV volume constructed by adding together all the area measurements of its body, occipital horns, and frontal and anterior horns (Penn *et al.* 1978). Third ventricle volumes were also calculated, with particular care taken to differentiate the inferior segment of the third ventricle from the inter-peduncular fossa. However, the superior and inferior limits of the third ventricle can be difficult to see clearly in some subjects so that, given its regular and slit-like shape, a single cross-sectional area taken from a slice through the middle of the ventricle might be regarded as the more valid measure. An estimate of intracranial volume was made by adding together the intracranial areas of four slices; the most superior slice on which the anterior horns alone were visible (vs), the slice below this and the two slices above. These slices, yielding a truncated intracranial volume henceforth referred to as simply 'intracranial volume', were chosen as the majority of the ventricle slices lay within them, and the relevant data were available on all subjects. The maximum areas of the lateral and third ventricles, and the corresponding intracranial area for that slice, were identified for each subject.

Sulcal area was measured, using the most superior slice that still contained lateral ventricular fluid, by tracing manually within the skull and cerebrum an annulus that contained

the entire cortical outline and sulcal spaces. The IVC summed all pixels between 0 and 25 HU inside this trace to give an estimated area of sulcal fluid. The boundaries of the interhemispheric fissure (IHF) were traced on the same slice and measured similarly. Right and left Sylvian fissures were defined manually, taking the most superior slice where the anterior horns were visible without the occipital horns or body of the LV coming into view. The areas were measured as for the IHF. Global visual ratings of the cortical sulcal spaces (0–3), the interhemispheric fissure (0–2) and the Sylvian fissures (0–3) were also made using reference photographs for each rating. This methodology is described elsewhere in greater detail (Owen *et al.* 1988; Harvey *et al.* 1990*a*; Jones *et al.* 1993*b*; Lewis, 1993).

Statistical analysis

Our analyses, involving expression of associations as odds ratios, and logistic regression models of the binary, case or control outcome, are unusual in the structural brain imaging literature, despite being appropriate methods for case–control studies (Breslow & Day, 1980). Sandercock (1989) has provided a general introduction to this approach with respect to the neurosciences, and the applicability of the techniques to psychiatry has been reviewed elsewhere (Lewis & Pelosi, 1990; Tsuang *et al.* 1992).

We divided the distribution of areas and volumes in the control group into thirds (tertiles). If there were no differences between cases and normal controls, a third of the cases, too, would have been found within each of these tertiles, and, with the lowest tertile as base line, the odds ratios equal to one. We tested the specific hypothesis that there would be a linear trend for cases to be found more frequently in higher tertiles. Adjustment was made for confounding factors using classical epidemiological statistics, such as those of Mantel & Haenszel (1959), and logistic regression analysis (Breslow & Day, 1980). Where analysis involved cases only, analysis of variance (ANOVA) was used. Analyses involved both area and volumetric measures so as to examine their relationship.

RESULTS

Of 317 eligible patients, 216 agreed to take part in this CT study. Sixty-seven controls were included.

The socio-demographic details of the case groups and controls are displayed in the top section of Table 1. The controls were of higher childhood socio-economic status than the cases, particularly those with schizophrenia, and contained more white European subjects although, in this age group, the proportion of such subjects in the controls was similar to that found in the local district. Cases and controls were scanned at similar ages but within the case groups, those with schizo-affective disorder had a later age at onset and more chronic course in terms of weeks as an in-patient. Controls had considerably higher verbal IQ than the cases (118 *v.* 103, 95% confidence interval (CI) difference 12·7–17·7, $P = 0{\cdot}001$). Men with schrizophenia had an earlier mean age at onset than did women (21·2 yr *v.* 25·2 yr, 95% CI difference 0·7–7·0 yr, $P = 0{\cdot}02$), whereas the ages at onset for men and women with schizo-affective and affective disorder were almost identical.

1. CT scan measures in the controls

Table 2 shows the intracranial and ventricular volumes for the controls. Men had larger intracranial and ventricle volumes, a reflection of their generally larger body size. There were trends (not significant) for white Europeans to have larger intracranial volumes but smaller ventricles. Those in higher socio-economic groups during childhood tended to have both larger cranial vaults and ventricles. The same patterns were observed for area measures. Thus, any differences in CT scan dimensions between cases and controls may have arisen either from the socio-demographic differences between them, or from true associations with the diseases under study; adjustment for these factors was necessary.

Correlations between age at CT scan and both ventricular and intracranial volumes were small (Table 2), and none was significantly different from zero. Intracranial volume was strongly associated with ventricle volume; correlations ranged from 0·25 to 0·44 for these measures, and all were statistically significant ($P < 0{\cdot}01$).

There were modest but statistically significant

Table 1. *Sociodemographic and clinical characteristics of the sample, and mean volumes for cases and controls (cm^3)*

	Controls	RDC schizophrenia	RDC schizoaffective	RDC affective*
Number	67	121	41	54
Male:Female (% male)	43:24 (64%)	91:30 (75%)	21:20 (51%)	19:35 (35%)
Childhood SES†				
I–II	49	29	12	21
III	12	44	15	14
IV–V	6	47	13	15
Ethnicity				
White European	61	64	20	18
Other	6	57	21	36
Age at CT scan (S.D.)	31·7 (6·9)	28·9 (8·1)	35·1 (9·4)	32·9 (8·8)
Verbal IQ‡ (S.D.)	118 (6·6)	101 (13·2)	105 (12·6)	106 (14·0)
Age at onset§ (S.D.)	—	22·7 (7·2)	25·1 (8·1)	23·3 (7·5)
Weeks as in-patient (S.D.)	—	29 (79)	49 (75)	26 (37)
Intracranial vol (cm^3)	655·8 (6·1)‖	637·7 (4·3)	619·0 (8·5)	617·9 (18·4)
Lateral ventricle vol	17·8 (15·3–20·3)¶	19·5 (17·6–21·5)	21·6 (17·7–25·5)	19·9 (12·8–26·9)
Third ventricle vol	0·91 (0·8–1·03)¶	1·03 (0·93–1·13)	1·03 (0·83–1·22)	0·93 (0·72–1·15)

Unadjusted intracranial volumes differ ($F = 4·4$, $P = 0·002$); ventricle volumes similar.
* 38 Mania/bipolar; 16 major depression.
† Childhood socioeconomic status (SES), recoded from Registrar General's classification (see text).
‡ From NART or verbal subset of WAIS (see text).
§ Age when first seen by a psychiatrist.
‖ Standard error of mean.
¶ 95% C.I. of true mean.

Table 2. *Ventricle volumes and sociodemographic features of the controls* (N = 67)

	Intracranial volume	Total lateral ventricle volume	Third ventricle volume
All controls (95% CI)	655·8 (643·8–667·8)	17·8 (15·5–20·2)	0·91 (0·78–1·03)
Sex			
Men	683·3	20·0	1·07
Women	606·7	13·9	0·61
95% CI diff.	59·6–93·5	1·1–11·0	0·23–0·7
	$P < 0·001$	$P = 0·02$	$P < 0·001$
Ethnicity			
White European	658·4	17·6	0·9
Other	629·5	20·1	0·87
95% CI diff.	−12·7–70·6	−0·6–11·2	−0·4–0·48
	$P = 0·2$	$P = 0·6$	$P = 0·8$
Childhood SES			
I–II	664·8	18·7	0·94
III	631·2	17·1	0·82
IV–V	631·8	12·3	0·84
F ratio	3·1 $P = 0·05$	1·1 $P = 0·3$	0·28 $P = 0·8$
Association with age at scan	$r = -0·03$	$r = 0·1$	$r = -0·03$
Association with verbal IQ	$r = 0·3$ $P = 0·04$	$r = 0·2$ $P = 0·15$	$r = 0·3$ $P = 0·02$

correlations between verbal IQ and both intracranial and third ventricle volume. Correlations between IQ and lateral ventricle measures were smaller and not significant. These associations between IQ and both cranial and third ventricle dimensions were confounded by sex and social class; all controls spoke English as their first language. Men and those in higher

Table 3a. *Odds ratios for tertiles of areas* (cm^2), *schrizophenia cases* versus *controls*

		Schizophrenia cases			
		Maximum lateral ventricle area		Maximum 3rd ventricle area	
	Controls *N*	*N*	Odds ratio	*N*	Odds ratio
Lowest tertile	22	29	1·0	30	1
Middle tertile	23	44	1·6	39	1·3
Highest tertile	22	48	1·7	52	2·0
Test for trend in odds ratios		$\chi^2 = 1{\cdot}98$ $P = 0{\cdot}2$		$\chi^2 = 3{\cdot}36$ $P = 0{\cdot}07$	
Odds ratio for linear trend (95% CI)		1·3 (0·9–1·9)		1·4 (0·98–2·1)	
As above – adjusted for maximum intracranial area		1·5 (1·01–2·3)		1·9 (1·2–2·9)	
As above – adjusted for intracranial area, sex, social class, ethnicity and age		2·2 (1·3–3·7) $P = 0{\cdot}005$		2·2 (1·3–3·8) $P = 0{\cdot}005$	
OR modelled as continuous variable and adjusted for intracranial vol, sex, class, ethnicity and age		1·1 (1·01–1·2) $P = 0{\cdot}03$ LRS* = 5·3, $P = 0{\cdot}02$		8·9 (2–40) $P = 0{\cdot}004$ LRS = 9·4, $P = 0{\cdot}002$	

* LRS = Likelihood ratio statistic (Breslow & Day, 1980).

social classes had larger heads (Table 2) and also scored better in the IQ assessments. Mean verbal IQ for men was 120, and for women 116 (95% CI for the difference 0·5–7·5, $P = 0{\cdot}03$). There was a gradient of IQ scores down from the higher socio-economic groups to the lowest. Using ANOVA, both sex and social class remained as significant independent effects on IQ (sex $F = 7{\cdot}02$, $P = 0{\cdot}002$; class $F = 4{\cdot}02$, $P = 0{\cdot}05$; no interactions).

2. Lateral ventricular volume in cases and controls

Table 1 (bottom section) shows the mean LV volume for all cases and controls. The distributions of all the area and volume measurements showed a slight positive skew. Log-transformation made very little difference and untransformed data were used throughout the analyses. There was a consistent pattern for controls to have significantly larger intracranial volumes than all the case groups ($P < 0{\cdot}05$ for all contrasts), whereas their ventricles were smaller, i.e. larger craniums containing brains with smaller ventricles. However, analysis of the controls alone demonstrated that these findings could have been the result of the differing socio-demographic and ethnic characteristics of cases and controls. Also, the strong correlations between intracranial volume and ventricle size demonstrated in the controls meant that the combination of smaller heads and larger ventricles found in the cases was unexpected, and that intracranial volume, too, must be taken into account when investigating dimensions of the ventricles. A very similar pattern of results were seen with area measurements.

(*a*) *Schizophrenia cases* versus *controls*

Results of the formal case–control analysis for schizophrenia are displayed in Table 3a for area measures, and Table 3b for volumes. The numbers of controls found in each tertile of the distribution of the LV and third ventricle is shown in the first column of figures in the tables. By definition, a third of the controls fell into each tertile. Had there been no difference between cases and controls, the cases would have been similarly distributed. They were not, as demonstrated by the increasing odds ratios in the middle and highest tertiles, compared to the lowest.

These raw, unadjusted linear trends were not statistically significant. Once adjustment was made (the next row) for the corresponding intracranial area/volume, the trend became more marked and statistically significant. Adjustment for sex, social class and ethnicity all improved the fit of the logistic regression model significantly, and resulted in a marked increase

Table 3b. *Odds ratios for tertiles of volumes (cm^3)*

	Controls	Schizophrenia cases					
		Lateral ventricle volume		Third ventricle volume		Intracranial volume	
	N	*N*	OR	*N*	OR	*N*	OR
Lowest tertile	22	27	1	31	1	52	1·0
Middle tertile	23	49	1·8	42	1·5	49	0·9
Highest tertile	22	45	1·7	48	1·6	20	0·4
Test for trend in OR		$\chi^2 = 1·6$ $P = 0·2$		$\chi^2 = 1·3$ $P = 0·3$		$\chi^2 = 3·8$ $P = 0·05$	
OR for linear trend		1·3		1·2		0·7	
As above – adjusted for IC volume		1·6		1·6			
As above – adjusted for IC vol, sex, age, social class, ethnicity		1·9 (1·1–3·2) $P = 0·02$		1·7 (1·02–2·8) $P = 0·04$		0·8* (0·4–1·4) $P = 0·4$	
OR modelled as continuous variable and adjusted as above		1·04 (1·02–1·7) $P = 0·04$		2·2 (1·04–4·7) $P = 0·04$		1·0 (0·9–1·04) $P = 0·2$	
Reduction in model deviance		LRS = 4·9 $P = 0·043$		LRS = 4·6 $P = 0·03$		LRS = 1·7 $P = 0·2$	

* Adjusted for sex, social class and ethnicity.
OR, odds ratio; IC, intracranial.

in the odds ratio for a linear trend in the ventricle size (next row), which remained statistically significant. The adjusted odds ratios for each stratum of maximum LV area in cases *versus* the control distribution were 1, 2·5 (0·9–6·8) and 4·5 (1·5–13·3), rather than the raw values of 1, 1·6 and 1·7, indicating why the trend became more marked once the confounding factors were taken into account. There was no evidence of significant interactions; in particular, no evidence that these effects were different in men and women. Graphical analysis of residuals (Cook & Weisberg, 1982) did not indicate that the relationship between schizophrenia and LV area would be better summarized by a model more complex than a simple, linear trend.

The final row in Table 3a, 3b shows the results from a separate logistic regression analysis where the ventricle size terms were modelled as continuous variables rather than as tertiles. Thus, as the maximum LV area increased by each 1 cm^2, so the odds ratio for cases *versus* controls having any particular value compared to the previous value, increased multiplicatively by 1·1. For example, cases would be $1·1^{10}$ (i.e. odds ratio of 2·59) times as likely as controls to have maximum LV area of 150 cm^2, than of 140 cm^2. That there was evidence of a linear trend meant that this effect operated throughout the range of measured values. There was no evidence of a threshold, or that there would be any bimodality in the distribution of the raw data. The significance of the likelihood ratio statistic (Breslow & Day, 1980) for total LV measures and third ventricle measures indicated that, in simple terms, regardless of the intracranial volume, sex, ethnicity and social class, these ventricle measures differentiated between cases and controls. The high value of 8·9 for the maximum third ventricle area occurred because this refers to an increase of 1 cm^2 in a structure of mean area 0·5 cm^2, a 200% increase. This problem comparing relative and absolute changes was avoided by the tertile analysis.

When LV and third ventricle volumes were both included in the same regression model, their effects were not statistically independent and remained similar to each other. The two dimensions were highly correlated ($r = 0·8$, $P < 0·001$); even quite large changes in one would result in predictable change in the other (Armitage & Berry, 1987) and no subject showed great disparity between the two.

Intracranial volume is examined in the final column of Table 3b. It appears from the unadjusted odds ratios that there was a significant trend for schizophrenic cases to have smaller intracranial volumes than controls. However, once confounding by socio-demographic factors was controlled, intracranial volume was not a

Table 4. *Lateral ventricle volume and third ventricle area, schizoaffective cases* versus *controls*

	Controls	Schizoaffective cases					
		Lateral ventricle volume		Third ventricle area		Intracranial volume	
	N	*N*	OR	*N*	OR	*N*	OR
Lowest tertile	22	8	1·0	13	1·0	25	1
Middle tertile	23	13	1·6	10	0·7	9	0·33
Highest tertile	22	19	2·4	17	1·5	6	0·25
Test for trend in odds ratios		$\chi^2 = 2·9$ $P = 0·09$		$\chi^2 = 0·8$ $P = 0·4$		$\chi^2 = 8·0$ $P = 0·01$	
OR for linear trend		1·5 (0·9–2·5)		1·4 (0·9–2·0)		0·5 (0·3–0·8)	
As above – adjusted for IC volume		2·5 (1·3–4·7)		2·6 (1·6–4·1)		–	
As above – adjusted for IC vol, sex, age, social class, ethnicity		3·3 (1·5–7·3) $P = 0·004$		3·4 (1·8–6·2) $P < 0·001$		*0·5 (0·2–1·3) $P = 0·2$	
OR modelled as continuous variable and adjusted as above		1·1 (1·02–1·1) $P = 0·006$		19 (4·8–72) $P < 0·001$		0·99 (0·9–1·1) $P = 0·2$	
Reduction in model deviance		LRS = 9·2 $P = 0·002$		LRS = 22·2 $P < 0·001$		LRS = 1·5 $P = 0·2$	

* Adjusted for sex, social class and ethnicity.
OR, odds ratio; IC, intracranial.

Table 5. *Affective disorder cases* versus *controls* (*third ventricle measures only*)

	Controls	Affective disorder cases			
		Maximum third ventricle area		Third ventricle volume	
	N	*N*	Odds ratio	*N*	Odds ratio
Lowest tertile	22	17	1·0	18	1·0
Middle tertile	23	15	0·9	13	0·8
Highest tertile	22	18	1·2	19	1·1
Test for trend in odds ratios		$\chi^2 = 0·2$, $P = 0·8$		$\chi^2 = 0·02$, $P = 0·9$	
Odds ratio for linear trend (95% CI)		1·2 (0·8–1·7)		1·0 (0·7–1·6)	
As above – adjusted for intracranial vol		1·7 (1·1–2·6)		1·4 (0·9–2·4)	
As above – adjusted for intracranial vol, sex, social class, ethnicity and age		1·8 (1·1–2·8) $P = 0·01$		1·5 (0·8–2·6) $P = 0·2$	
Modelled as continuous variable and adjusted for IC vol, sex, class, ethnicity and age, OR (95% CI)		8·1 (2·4–2·8) $P < 0·001$ LRS = 11·9, $P < 0·001$		2·1 (0·9–5·1) $P = 0·1$ LRS = 2·7, $P = 0·1$	

No evidence of differences between cases and controls for lateral ventricles, anterior horns or intracranial size.
OR, odds ratio; IC, intracranial.

significant discriminator; the smaller intracranial volume in schizophrenic cases was likely to have been secondary to, although not necessarily caused by, the ethnic composition and the lower childhood social status of this group.

In summary, there was a linear trend for schizophrenic cases to have larger lateral and third ventricles than controls, independently of intracranial size, sex, childhood social class and ethnicity. Intracranial size alone did not differentiate cases from controls.

(*b*) *Schizo-affective disorder* versus *controls*

The results for lateral ventricle volume and third ventricle area in schizo-affective disorder are presented in Table 4, just as for schizophrenia,

Table 6. *Obstetric complications and family history in schizophrenia and schizoaffective disorder cases*

	Obstetric complications		Family history of schizophrenia or schizo-affective		Family history of affective disorder		Family history of any FH-RDC disorder*	
	Absent ($N = 87$)	Present ($N = 34$)	Absent ($N = 138$)	Present ($N = 24$)	Absent ($N = 123$)	Present ($N = 39$)	Absent ($N = 87$)	Present ($N = 75$)
Total lateral ventricle volume (mean vols cm^3)								
Unadjusted	21·2	18·3	20·6	16·8	19·8	20·9	20·3	19·8
F ratio†	$F = 4·9$, $P = 0·03$		$F = 2·5$, $P = 0·1$		$F = 0·1$, $P = 0·8$		$F = 0·01$, $P = 0·9$	
Maximum third ventricle area (mean areas, cm^2)								
Unadjusted	0·64	0·62	0·64	0·51	0·59	0 65	0·59	0·61
F ratio	$F = 1·2$, $P = 0·3$		$F = 3·5$, $P = 0·06$		$F = 2·7$, $P = 0·1$		$F = 0·7$, $P = 0·5$	

* Includes FH-RDC cases of schizophrenia, schizoaffective disorder, bipolar disorder, unipolar depression, other psychosis, suicide and psychiatric disorder NOS.

† ANOVA controlling for headsize/intracranial area, age, sex, social class and ethnicity.

and the pattern of results was the same. There were significant trends for the schizo-affective cases to have larger ventricles independent of intracranial volume and other confounders. The effect sizes (magnitude of the odds ratios) were slightly greater than for the schizophrenia group, although the 95% confidence intervals show considerable overlap between the two groups. Closely comparable findings were obtained using LV area or third ventricular volume and, for the sake of brevity, these data are not presented. Thus, in terms of associations with the ventricle sizes, RDC schizophrenia and schizo-affective disorder cases were very similar.

(c) *Affective psychosis* versus *controls*

There was no evidence of an association between LV size and affective psychosis; the distribution of the cases was almost identical to that of the controls, the odds ratios showed no patterns, and none was significantly different from unity. For instance, in the case of total lateral ventricle volume, the adjusted OR for linear trend was only 1·1 (0·65–1·9, $P = 0·7$).

This was not the case for the third ventricle (Table 5). Increasing third ventricle area (adjusted trend OR = 1·8, 95% CI 1·1–2·8, $P = 0·01$) showed a statistically independent association with affective psychosis. The size of this effect was similar to the other two diagnostic groups, as was the effect size for third ventricle volume (OR = 1·5, 95% CI 0·8–2·6) but the latter was not statistically significant.

(d) *Extra-cerebral CSF*

The distributions of the areas for sulcal fluid, interhemispheric fissure and the Sylvian fissures were all highly positively skewed, the modal values being zero, and parametric analysis was not possible. No significant differences between the controls and any of the case groups were demonstrable with Mann–Whitney tests, neither did logistic regression analysis reveal any significant associations, or patterns in the results. This negative result was also found when the global visual ratings were analysed. The difference between left and right Sylvian fissure areas (L–R) gave a normally distributed measure of Sylvian fissure laterality (control mean 0·04, 95% CI 0·02–0·06). There was no association between laterality and any case group *versus* controls.

3. Possible determinants of ventricle size – obstetric complications and family history

The similarity between the schizophrenic and schizo-affective cases, in terms of the analyses of ventricle size, permitted them to be combined into a single group; the pattern of results was identical for either group alone.

In schizophrenia and schizo-affective disorder combined, definite obstetric complications were slightly more prevalent, but not significantly so, in men than in women (combined diagnoses: men 30% *v.* women 22%, OR = 1·5, 95% CI 0·6–4·00), in higher socioeconomic groups (χ^2

Table 7. *Obstetric complications and family history in affective disorder cases*

	Obstetric complications		Family history of schizophrenia or schizo-affective		Family history of affective disorder		Family history of any FH-RDC disorder*	
	Absent ($N = 32$)	Present ($N = 7$)	Absent ($N = 48$)	Present ($N = 6$)	Absent ($N = 39$)	Present ($N = 15$)	Absent ($N = 33$)	Present ($N = 21$)
Total lateral ventricle volume (mean vols cm^3)								
Unadjusted	18·0	27·7	17·7	21·9	19·5	14·7	18·9	17·0
F ratio†	$F = 6·2$, $P = 0·02$		$F = 1·02$, $P = 0·3$		$F = 1·4$, $P = 0·2$		$F = 0·1$, $P = 0·8$	
Maximum third ventricle area (mean areas, cm^2)								
Unadjusted	0·57	0·76	0·58	0·61	0·64	0·54	0·60	0·61
Adjusted†	0·59	0·66	0·58	0·61	0·63	0·54	0·61	0·59
F ratio	$F = 0·4$, $P = 0·5$		$F = 0·1$, $P = 0·8$		$F = 1·0$, $P = 0·3$		$F = 0·03$, $P = 0·9$	

* Includes FH-RDC cases of schizophrenia, schizoaffective disorder, bipolar disorder, unipolar depression, other psychosis, suicide and psychiatric disorder NOS.

† ANOVA controlling for headsize/intracranial area, age, sex, social class and ethnicity.

trend 1·5, $P = 0·2$) and in white Europeans (OR = 2·04 95% CI 0·9–4·04). In affective disorder, the associations between OCs and sociodemographic variables were similar to the schizophrenia group but none was statistically significant.

Mean volumes of the LV and third ventricles in schizophrenia/schizo-affective disorder and affective disorder cases are shown in Tables 6 and 7 respectively, broken down by the presence of obstetric complications (OCs) and family history. The *F* ratios presented in the Tables refer to the main effect of OCs or family history in an ANOVA including age at scan, sex, ethnicity and socioeconomic group at birth.

All schizophrenia/schizo-affective cases, regardless of their OC or family history status showed the pattern of larger ventricles than controls, but the mean lateral ventricle sizes differed between these sub-groups of cases when they were compared to each other (Table 6). LV volume was smaller in schizophrenia/schizo-affective cases with a history of OCs than in those without, but no significant effect was seen for the third ventricle. Those with a positive family history of schizophrenia or schizo-affective disorder also showed this pattern of smaller lateral and third ventricles than those with a negative family history, but this may have been due to chance. In all cases, there was no evidence of an association between family history of schizophrenia/schizo-affective disorder and OCs (OR 0·9, 95% CI 0·3–3·1). When cortical sulci were analysed in terms of visual ratings, no contrast approached statistical significance; the majority (> 80%) of cases were judged to have normal or minimally enlarged extra-cerebral spaces whether they were categorized in terms of OCs or the definitions of family history.

In affective disorder, the results regarding cerebral ventricle volumes and OCs were in the opposite direction (Table 7) to the schizophrenia group, although the number of cases with OCs was small. Cases with OCs had significantly larger LV than those without but, as in the schizophrenic group, no effect was seen for the third ventricle. Differences for family history were small and not significant. There was no evidence that these effects were different in men and women.

4. Clinical correlates of ventricle dimensions in schizophrenia and schizo-affective disorder

(*a*) *Chronicity*

The general pattern of associations between lateral and third ventricle volumes, and schizophrenia and schizo-affective disorder was unchanged when the analyses were restricted to first admissions ($N = 47$). For instance, for schizophrenia alone (compare Table 3b), restriction of the analysis to cases scanned during their first admission resulted in an unadjusted OR for linear trend in the association between LV volume and schizophrenia of 1·2, and of 1·4 for third ventricle volume. There was no large or significant correlation between ventricle volume and either number of previous admissions or weeks as an in-patient prior to index admission.

Two further measures of chronicity were investigated. First, the time from first contact with psychiatric services until CT scanning was calculated. There was no evidence of a significant association with LV volume or third ventricle area, either in a simple scatter plot or in a multiple linear regression model controlling for intracranial size, sex, social class and ethnicity. Secondly, for subjects other than those scanned during their first admission to hospital, the proportion of time since first contact spent as an in-patient was calculated and analysed in the same way. Once again, no association was evident between ventricle dimensions and this composite chronicity–severity variable.

(*b*) *Age at onset*

There was no evidence in simple scatter plots of a significant negative association between age at onset and LV volume for either sex. In fact, the regression lines indicated a weak positive relationship (men, age at onset = 0·08 × LV volume + 20, $P = 0{\cdot}3$); younger onset was associated with smaller ventricles. We explored this further using a multiple regression model including sex, social class, ethnicity and intracranial volume. Sex remained the only significant variable, having a coefficient of 3·5 ($t = 2{\cdot}7$, $P = 0{\cdot}007$); females had a later age at onset regardless of ventricle size or social characteristics.

(*c*) *Pre-morbid social adjustment*

No associations were demonstrated between premorbid social adjustment and ventricle dimensions in the total psychosis group, or in any diagnostic groups alone. This negative finding was unaffected by the method of analysis; unadjusted ventricle volume did not correlate with pre-morbid social adjustment ($r = -0{\cdot}1$, $P = 0{\cdot}4$), neither did ANOVA (when controlled for head-size, sex, ethnic group or social class) reveal any evidence of an association between pre-morbid social adjustment and lateral ventricle volume ($F = 0{\cdot}2$, $P = 0{\cdot}8$).

DISCUSSION

Our analytical approach has avoided confusion over the considerable overlap between ventricle size in cases and controls, and the problem of defining 'enlargement'. The results demonstrated that, regardless of sex, age, intracranial volume, social class or ethnicity, cases with schizophrenia or schizo-affective disorder are more likely than controls to have larger ventricles. For affective psychosis, this effect appeared to be confined to the third ventricle. Within the diagnostic case groups, obstetric complications were significantly associated with smaller lateral ventricles in schizophrenia, and larger ventricles in affective psychosis.

Methodological issues

It is unlikely that our cases are biased towards those having particularly large ventricles; the majority of local cases of schizophrenia are admitted to hospital and the minority who are not, differ little from those who are (Castle *et al.* 1994). We attempted to collect CT scan data on all cases eligible, and have no reason to believe that the subjects who refused to have a scan were a special group in terms of ventricle size. The sample comprised mainly (84%) cases from local catchment areas but also included tertiary referrals, who were perhaps more likely to have severe illness and larger ventricles. An analysis not presented here, indicated this was not the case. The cross-sectional nature of the survey raises the possibility that chronic cases with large ventricles influenced our results. The finding of no association between ventricle size and chronicity of schizophrenia is evidence against this. In accordance with the view that age-related ventricle changes make appreciable impact only after 50–60 years (Zatz *et al.* 1982; Pfefferbaum *et al.* 1988; Stafford *et al.* 1988; Pearlson *et al.* 1989), age correction made no difference to the results in this study, where 97% of the subjects, including affective psychotics, were under 50 years.

With regard to possible confounding by ethnicity, restriction of the analysis to white Europeans was not feasible due to the high proportion of cases from other ethnic groups, predominantly Afro-Caribbeans. We decided to assume that our non-white controls were representative of these ethnic groups, and to control for confounding using the regression methods described. We did not control for verbal intelligence. Both intellectual function and psychosis are undoubtedly linked to brain structure; to have matched for cerebral function in terms

of IQ might have obscured the association of interest between psychosis and ventricle size (Gur *et al.* 1991; Resnick, 1992; Jones *et al.* 1993*a*; Jones & Rodgers, 1993). Also, the case groups included individuals where English was not the first language. This may have reduced the estimated IQ.

Although by no means immune from criticism, this study has several strong points. It is, to our knowledge, one of the largest published series of CT scans in the functional psychoses (Takahashi *et al.* 1981; Sacchetti *et al.* 1992), and the only large series to attempt to minimize patient selection bias by including all suitable consecutive admissions, and to have used automated image analysis. Clinically, each patient was assessed in depth, with an independent informant where possible. The controls were a volunteer sample, not 'super-normal' and allowed the control of common confounders. Lastly, the use of an analysis based on the population distribution may have heuristic value.

Findings

Perhaps the most important of our findings are from the odds ratio analysis of ventricle size in cases and controls. Although the notion of large ventricles is widely accepted in schizophrenia, our analysis allows more to be concluded than just a statement or a significant group difference. First, since it generates a level of risk, or probability, the result from each comparison can be expressed in a universal quantity (odds ratio) which can be compared in magnitude to quite different aetiological factors such as the season of birth effect (OR $\simeq$ 1·1) and genetic predisposition (OR $\simeq$ 10). Secondly, and for the same reason, it also allows relative weight to be given to different anatomical abnormalities; both LV and third ventricular enlargement in schizophrenia carry odds of approximately 2·0 and should be given equal priority in further attempts to understand their origin. Thus, with MRI, if the odds for temporal horn enlargement in schizophrenia greatly exceeded that for the overall LV, present efforts to concentrate more on the former (DeGreef *et al.* 1992) would be justified.

Thirdly, the finding of a significant linear trend across the three tertiles indicates that the association between schizophrenia and ventricle size is not confined to a subgroup of cases with very large ventricles; in that case the odds would be increased just across the upper tertile. This is in agreement with results from frequency distribution analyses (Harvey *et al.* 1990*a*; Daniels, 1991), which find no evidence of bimodality, and studies of both discordant monozygotic twins (Reveley *et al.* 1982; Suddath *et al.* 1990) and sibling pairs (Weinberger *et al.* 1981; DeLisi *et al.* 1986). In these studies, affected cases do not represent a homogeneous subgroup of brain structural abnormality but are merely each different from their twin or sibling. Thus, the overlap between the ventricle sizes of cases and controls (Shelton & Weinberger, 1986; Iacono *et al.* 1988; Birley, 1992) is explained, and the problems of defining 'enlargement' avoided. The increased risk conferred by increasing ventricle size is not confined to those with the largest ventricles, it is continuous throughout the population. The findings of overlap in distributions of ventricle size and the lack of evidence in favour of bimodality (Harvey *et al.* 1990*a*) cease to be a puzzle in this framework; they are to be expected, as is the corollary, that most subjects with schizophrenia will have ventricle size within the normal range. Indeed, the ultimate conclusion from these strands of evidence would be that it is not a sub-group, but all people with schizophrenia who have enlarged ventricles: each case has slightly larger ventricles than expected, had they not had schizophrenia.

Finally, the increase in odds ratio observed for schizophrenia was modest; ventricle size is a statistically independent risk factor, but one of moderate size. The association should be judged as very unlikely to be a direct causal one, and it can readily be seen that Type II errors might be common in smaller samples.

The control group confirmed both the well established, normal gender difference in intracranial volume, and the entwined influences of IQ, social class and cranial size – a problem that remains unresolved in structural MRI research (Andreasen *et al.* 1990*b*, 1993; Zipursky *et al.* 1991). We demonstrated no difference in cranial size between cases and controls once socio-demographic factors were controlled. We do not interpret our finding of a relationship between head-size, social class and IQ within the controls as sufficient evidence of cause and effect. On the contrary, there is evidence of a strong relationship between social advantage and general body

dimensions (Tizard, 1975) which may be quite independent of that between social class and educational achievement. This raises the possibility that similar confounding occurs in neuropathological studies and suggests that more attention should be given to the relationship between sociodemographic characteristics and brain structure on a cytoarchitectural level. Regarding gender, we made an *ad hoc* decision to test for gender differences in the association between ventricle size and RDC psychoses by fitting 'sex*ventricle size' interaction terms in the logistic regression models. None approached statistical significance and we conclude that there was no evidence that the associations we demonstrated between cases and ventricle dimensions were different in men and women.

Structural brain changes in affective disorder have received less attention in the literature than is the case for schizophrenia. In the present study, the group of affective psychotics showed no evidence of LV enlargement in either sex, but were significantly more likely than controls to have large third ventricles. Although some earlier CT studies strongly implied that there was LV enlargement in patients with affective illness, this has not been a consistent finding (Scott *et al.* 1983; Dolan *et al.* 1985; Schlegel & Kretzschmar, 1987; Andreasen *et al.* 1990*c*) and has become increasingly uncertain with recent MRI reports (Johnstone *et al.* 1989*a*; Swayze *et al.* 1990; Coffey *et al.* 1993). The affective patients in this sample all had positive psychotic symptoms, previously associated with greater structural change (Scott *et al.* 1983; Targum *et al.* 1983; Lutchins *et al.* 1984; Sacchetti *et al.* 1987; Schlegel & Kretzschmar, 1987), so one might conclude that the absence of LV enlargement is all the more convincing. This is particularly so, given that the diagnostic misclassifications with schizo-affective disorder and schizophrenia would be more likely in such a group.

In regard to third ventricle size in affective psychosis, previous CT results have been similarly inconsistent (Schlegel & Kretzschmar, 1987; Dewan *et al.* 1988; Iacono *et al.* 1988). The marked discrepancy between the lack of association with LV size and the definitive association between affective disorder and increasing third ventricle size indicates this was a real phenomenon; it was not that, in a small sample, one result was statistically significant whereas the other just fell short. In a recent MRI study, Coffey *et al.* (1993) demonstrated that subjects with affective disorder referred for electroconvulsive therapy had both larger lateral (18%) and third ventricle (6%) volumes, although the results for their sample ($N = 47$) were not significant. They comment that their data are compatible with a third ventricle volume increase of up to 30%, so our results are not contradictory. Their effects were corrected for educational status which, we believe, would have been an additional reason for their best estimate to be biased towards the null. We argue that structural changes do occur in affective psychosis but over a more restricted area (primarily the diencephalon) than in schizophrenia. In terms of risk, it is possible that such changes, betrayed by large third ventricles, are relevant to psychosis in general, rather than to any particular diagnosis. Studies on larger, more representative samples of affective disorders, including milder forms, would be useful here in that predictions could be made as to how associations would change as the case mix varied. However, we believe that there is enough evidence to suggest that attention is best diverted away from LV size in affective disorder if abnormalities are proving so elusive (Coffey *et al.* 1993).

Correlates of ventricle size

In contrast to the findings in the formal case–control analysis, our results were less clear regarding correlates of ventricle size within the case groups alone. The confirmation of no association between duration of illness and ventricle size is important, and supports results from first episode CT studies (Turner *et al.* 1986) and four follow-up studies (Nasrallah *et al.* 1986; Illowsky *et al.* 1988; Reveley *et al.* 1988; Vita *et al.* 1988). Nasrallah and colleagues demonstrated considerable variability in VBR at the second, follow-up scan, possibly a consequence of the smaller 'sample' of measures used in studies of area, compared with studies using volumes calculated from several slices. Two recent MRI studies employing volume measurements (Degreef *et al.* 1991; DeLisi *et al.* 1992) support this contention and the finding of lack of progression. The importance of the apparent lack of association between LV volume and chronicity lies in the implication that the

determinants of the size are active early in life and by inference, that the modification of risk for schizophrenia also occurs early.

Of the studies looking for an association between family history and ventricle size, five have reported an inverse correlation between ventricular size and positive family history (Reveley *et al.* 1984; Cazullo *et al.* 1985; Turner *et al.* 1986; Romani, 1987; Owen *et al.* 1989). One study found a positive correlation (Nasrallah *et al.* 1983) and one evidence of a curvilinear correlation (Owens *et al.* 1985). Most reports have found no relationship (Pearlson *et al.* 1985, 1989; Kemali *et al.* 1986; Farmer *et al.* 1987; Nimgaonkar *et al.* 1988; Johnstone *et al.* 1989*b*; Kaiya *et al.* 1989; Reddy *et al.* 1989; Andreasen *et al.* 1990*a*). Our own investigation, like other studies, relied on the family history method, with the inherent likelihood of misclassification, and had no data for normal controls. It did have available a larger sample size than all the negative studies. We consider that the present results offer little support for the inverse relationship in schizophrenia between family history of the disorder and ventricle size, and no support for the hypothesis that a family history of affective disorder may be associated with small ventricles in schizophrenia (Owen *et al.* 1989); if true effects do exist, they are likely to be minor.

Our lack of normative control data hinders interpretation of the contrary findings regarding OCs and ventricle volume in schizophrenia and affective psychosis. We believe it is most unlikely that OCs might have opposite effects on LV volume in the two conditions, particularly as we demonstrated no evidence of an effect on the third ventricle in either diagnostic group. As for family history, presence or absence of OCs is likely to represent a crude classification of early environmental risk factors, and the most parsimonious conclusion from our data is that the nature of the true associations between such factors and ventricle volume remains unclear (Lewis, 1990). However, given that the size and nature of any association between OCs and psychosis has been questioned recently (Lewis, 1990; Done *et al.* 1991; Buka *et al.* 1993), our results do not support the proposition that the group of obstetric complications, as defined here, are the proposed environmental factor particularly associated with large ventricles in schizophrenia (Lewis *et al.* 1987).

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Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort

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Summary

Schizophrenia has been linked with childhood psychological abnormalities since it was first described, but studies of associations have not used population samples and so may be subject to bias. We have studied associations between adult-onset schizophrenia and childhood sociodemographic, neurodevelopmental, cognitive, and behavioural factors within a cohort of 5362 people born in the week March 3–9, 1946. Childhood data were gathered prospectively and case ascertainment was independent of routine follow-up of this cohort.

30 cases of schizophrenia arose between ages 16 and 43 years (cumulative risk 0·63% [95% CI 0·41–0·86%]). Milestones of motor development were reached later in cases than in controls, particularly walking (difference in means 1·2 months [0·1–2·3], p=0·005), and up to age 15, cases had more speech problems than had controls (odds ratio 2·8 [0·9–7·8], p=0·04). Low educational test scores at ages 8, 11, and 15 years were a risk factor, with significant linear trends across population distributions; risk was not confined to very low scores. Solitary play preference at ages 4 and 6 years predicted schizophrenia (odds ratios 2·1, 2·5, p=0·05). At 13 years cases rated themselves as less socially confident (p for trend, 0·04). At 15 years, teachers rated cases as being more anxious in social situations (p for trend 0·003), independent of intelligence quotient. A health visitor's rating of the mother as having below average mothering skills and understanding of her child at age 4 years was a predictor of schizophrenia in that child (odds ratio 5·8 [0·8–31·8], p=0·02).

Differences between children destined to develop schizophrenia as adults and the general population were found across a range of developmental domains. As with some other adult illnesses, the origins of schizophrenia may be found in early life.

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Introduction

Genetic or environmental, the seeds of schizophrenia seem to be sown during early life. The disorder has been linked with childhood psychological abnormalities since it was first described and studies of neuropathology,[1] pregnancy and delivery complications,[2] and associations with prenatal exposure to influenza[3] and malnutrition[4] suggest that causal factors might operate in utero. People who develop schizophrenia seem to have impaired intelligence in childhood[5] and subtle differences in social[6,7] and neurological[8,9] development have also been reported. Evidence of fetal or childhood abnormalities in about a third of adults with schizophrenia has given rise to the suggestion of a distinct, neurodevelopmental subtype of the disorder.[10]

It is difficult, however, to demonstrate associations between early developmental events and adult outcomes, and the view of schizophrenia as a developmental disorder has gained somewhat capricious support.[11] Few studies have used general population samples, so are subject to selection and information biases; even studies of spontaneous, contemporary comments on children may be limited by the expectations of the commentator, which may differ between, for example, girls and boys.[12] In all designs, complex behavioural events are commonly dichotomised simply as normal or abnormal.

In this study, prospective data on a general population birth cohort followed for 4 decades enabled us to investigate associations between adult-onset schizophrenia and childhood behavioural, social, intellectual, and developmental characteristics, with less bias. We also investigated the distribution within the general population of risk conferred by continuous factors, such as childhood intelligence quotient (IQ) and personality ratings.

Methods

The sample comprised the Medical Research Council National Survey of Health and Development (NSHD), a stratified, random sample (5362) of a survey of 13 687 births in England, Scotland, and Wales during the week March 3–9, 1946.[13,14] The NSHD is the first of three British birth cohorts, the others comprising subjects born in the same week of March in 1958 and 1970. Follow-up continues. Difficulties arising from the rarity of schizophrenia as an outcome are offset by the high rate of follow-up achieved throughout childhood (average 91% follow-up during ten contacts between ages 2 and 15 years),[15] the long duration of the survey, and by case finding procedures independent of sample attrition. This analysis used a risk set of all survey members alive in the UK at age 16 years (4746).

Cases of schizophrenia arising between ages 16 and 43 years were identified in two stages, with childhood information not known.

programme but also regular contact with health professionals both at the hospital and at home.

Many issues concerning rehabilitation require further evaluation. These include the contributions of the various components of the programme, the mechanism of improvement, the appropriate setting, and the length and frequency of follow-up visits. Evidence that respiratory rehabilitation is effective was equivocal, so we selected a comprehensive, fully supervised programme, which was expensive (about Canadian $12 000 per patient). An outpatient programme would be cheaper and encouraging results have recently been reported from a community-based programme in which subjects were supervised by a family practitioner, nurse, and physical therapist.[33]

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The first stage used three sources to identify survey members for whom there was any evidence of schizophrenia, severe unclassified mental illness, a psychiatric hospital admission, or antipsychotic drug use. First, we used the nine questionnaire and interview contacts made between 16 and 43 years of age enquiring into hospital contacts, general practice visits, and survey members' descriptions of their illnesses. The second source was the Mental Health Enquiry (MHE) in England, Wales, and Scotland. MHEs are central registers of all admissions to psychiatric hospitals and include discharge diagnosis according to the contemporaneous International Classification of Diseases codes. The English and Welsh register was active from 1974 to 1986, that in Scotland still continues. Thirdly, a short version of the present state examination (PSE)[16] was administered at age 36.

In the second stage, DSM-IIIR[17] criteria for schizophrenia or schizoaffective disorder were applied to clinical material extracted from hospital case notes, correspondence with general practitioners, and survey members' own descriptions recorded during routine interviews. To investigate bias from misclassification, cases were classified according to certainty of diagnosis into those who satisfied DSM-IIIR criteria for schizophrenia or schizoaffective disorder, and those for whom positive DSM-IIIR criteria were satisfied, but no statement could be found of relevant exclusion criteria. Control subjects were defined as the remainder of the risk set without cases of schizophrenia.

Data on this cohort were collected eleven times between ages 6 weeks and 16 years, and nine times thereafter, most recently at age 43 (1989). Thus, some 2000 childhood variables were available for analysis. To avoid spurious positive findings, and guided by published results, we selected 54 variables from the period between ages 6 weeks and 16 years from four domains that were analysed separately.

Sociodemographic Variables included social class, defined as the Registrar General's Classification[18] of father's occupation in 1946 and 1961, and the municipal characteristics of birth place, as well as health visitors' comments on home, child, and mother.

Timing of early milestones (sitting, standing, and walking unaided, teething, and saying words other than names for the parents) was as recalled by the mother at age 2. We also included height, weight, and observations of speech made during medical examinations at ages 6, 7, 11, and 15 years.

Educational achievement In group tests non-verbal, verbal, and reading abilities were measured at ages 8, 11, and 15 years, arithmetic at ages 11 and 15 years, and vocabulary at ages 8 and 11 years.[19,20]

Sociobehavioural This category included mothers' structured comments on the child's play preference at ages 4 and 6. At age 13, children completed the Pintner aspects of personality inventory, which gives four continuous measures:[21] *emotional stability* (eg, "I often feel sad for no reason at all", "I worry about the little mistakes I make"), *sociability* (eg, "I make friends easily", "I feel at home at parties"), *negative attitudes to others* (eg, "I find that very few people can be trusted", "I often get blamed for things I didn't do"), and *aggressive behaviour* (eg, "I have a right to fight for what I want", "I sometimes feel like hitting people"). Teachers' questionnaires completed when the children were 15 years old produced three factors: *antisocial* ("frequently disobedient", "evades the truth"), *anxious* ("tired and washed-out", "timid child", "frightened of rough games"), and *habits* (nail-biting, nervous twitches).

Associations between schizophrenia and childhood variables were expressed as odds ratios (with 95% CI) adjusted for confounding by sex and social class by maximum likelihood logistic regression; for variables up to age 8, social class at birth was used, later that at age 15. Initial analysis of continuous variables was done by dividing their distributions into tertiles and assessing deviation from linear trends in associations. Asymptotic hypothesis tests were two-sided and 95% CI were calculated by exact methods, a conservative approach accounting for some limits including 1, while $p < 0.05$. Results for all variables examined are presented.

Results

Of 4746 (2477 male, 2269 female) individuals in the risk set, 81 were identified as potential cases in the first stage of screening. Subsequently, 30 (20 men, 10 women) were classified as cases of schizophrenia; 22 (73%) were in the more confident diagnostic group. 2 (7%) cases had no record of hospital admission. Controls were the remaining 4716 subjects. The risk of schizophrenia up to age 43 was 0·63% (95% CI 0·41–0·86); the risk was greater for men than for women (0·88 *vs* 0·44%; odds ratio 1·8 [0·9–3·9]). The mean age at onset was 24·3 years (95% CI 21·5–27·0; median 21·5 years; range 17–43 years); the mean age was earlier in men than in women (23·4 *vs* 25·9 years; difference 2·5 years [95% CI −3·3 to 8·2] $p = 0.3$).

Sociodemographic characteristics

There was no evidence that low social class at birth was associated with later schizophrenia; a non-significant trend was found in the opposite direction (χ^2 test, $p = 0.1$). There was no association between later schizophrenia and either the administrative characteristics (eg, urban/rural) or population size of the place of birth.

A four-point measure of home circumstances, derived from health visitors' reports when the child was 4 years old of the state of housing, crowding, cleanliness of house and child, and a subjective rating of mothering skills[22] was consistent with the impression of slightly higher risk of schizophrenia in children from more advantaged homes ($p = 0.08$). This advantage was apparent for all constituent items except one. By health visitors' ratings more mothers of cases than of controls had worse than average general understanding and management of their children (odds ratio 5·8 [0·8–31·8] $p = 0.02$). At that time, no case mother was known to be mentally ill.

Developmental milestones and physical development

The mean ages at which speech and gross motor milestones were reached were later for cases than for controls (table 1). The greatest difference was for walking, an effect which achieved statistical significance ($p = 0.005$) and which was independent of sex and social class (likelihood ratio statistic = 6·7, $p = 0.01$).

On health visitors' records, at age 2 years, a higher proportion of cases than of controls had not attained all the milestones of talking or sitting, standing, and walking alone (2/27 cases *vs* 64/3918 controls; odds ratio 4·8 [1·3–17·9] $p = 0.02$). The 2 cases had not attained speech, whereas there was an even spread of delayed milestones for controls. At age 6, doctors noted non-structural speech problems in 3 cases (11·1%; not the 2 children who were not talking at age 2) compared with 212 (5·1%) controls (2·2 [0·7–7·3], $p = 0.2$) but by age 15, only 1 case was noted as having problems (a stammer). Thus, between ages 2 and 15 years, speech problems were more frequent in cases than in controls (2·8 [0·9–7·8], $p = 0.04$).

Milestone	Modal value	Control mean (SD)	Case-control difference (95% CI)
Sitting	6	6 5 (1 5)	0 1 later (0 5 earlier–0 8 later)
Standing	12	11 4 (2 2)	0 2 later (0 6 earlier–1 0 later)
Walking	12	13 5 (2 4)	1 2 later (0 1 later–2 3 later)
Teething	6	6 8 (2 2)	0 2 earlier (1 0 earlier–0 6 later)
Talking	18	14 3 (4 2)	1 2 later (0 4 earlier–2 8 later)

Table 1: **Age (months) at developmental milestones: mothers' recall when child was 2 years old**

Test and age (years)	Case mean (SD)	Mean deficit shown by cases* (% 1 SD)	F ratio†	p
Non-verbal				
8	97 0 (14 1)	5 9 (39%)	3 8	0 05
11	98 9 (16 7)	4 4 (29%)	2 1	0 14
15	93 6 (15 9)	9 5 (63%)	9 9	0 002
Verbal				
8	96 6 (15 4)	7 1 (47%)	5 7	0 02
11	97 3 (15 8)	5 2 (35%)	3 3	0 07
15	96 3 (12 5)	7 5 (50%)	6 5	0 01
Arithmetic/mathematics				
11	97 6 (16 4)	6 1 (41%)	5 1	0 02
15	99 2 (13 6)	6 9 (46%)	5 7	0 02
Vocabulary				
8	100 8 (17 7)	3 1 (21%)	1 1	0 3
11	99 8 (14 6)	4 5 (30%)	2 3	0 2
Reading				
8	99 6 (16 3)	4 0 (27%)	1 8	0 2
11	100 1 (14 6)	4 5 (30%)	2 3	0 2
15	100 2 (12 7)	3 5 (24%)	1 5	0 2

*Corrected for confounding by sex and social class by multiple classification analysis. Risk set means ⩾100 due to differential sampling of NSHD.
†ANOVA including sex and social class: main effect of case vs control. No sex case interaction was significant.

Table 2: **Mean deficits shown by cases in educational test scores: normalised scores based on sample mean 100, SD 15**

There was no evidence of differences between cases and controls in mean birthweight, or height and weight at ages 7 and 11 years; no case fell outside the range of two standard deviations around the control mean. Age at puberty and the attainment of bladder and bowel control was very similar in the two groups.

Educational achievement

Mean scores in all educational tests at ages 8, 11, and 15 years were consistently lower for cases than for controls (table 2). Adjusted for confounding by sex and social class, the deficits were greatest for verbal, non-verbal, and mathematical skills, and least for vocabulary and reading. Inspection of frequency distributions revealed no evidence of a subgroup of cases with very low scores.

The first principal component of the scores, accounting for some 75% of the total variance, was derived at each age. When distributions of these scores were divided into tertiles, cases were consistently over-represented in the lowest test scores, and were progressively less likely to be found in the middle and highest thirds of ability (table 3). Summarised by the odds ratio for linear trend (ie, that associated with moving one category), this effect seemed to become stronger with age, the trend at age 15 being

	Population distribution of IQ†			Summary odds ratio for linear trend in association‡ (95% CI)
	Lowest tertile	Middle tertile	Highest tertile	
Age 8 years				
Number of cases	11	7	6	..
Adjusted odds ratio*	1	0 6	0 5	0 7 (0 4–1 2) p=0 2
Age 11 years				
Number of cases	14	6	6	..
Adjusted odds ratio*	1	0 5	0 4	0 6 (0 4–0 99) p=0 04
Age 15 years				
Number of cases	13	8	4	.
Adjusted odds ratio*	1	0 6	0 3	0 5 (0 3–0 9) p=0 01

*First principal component derived from all test scores at each age.
†One third of controls in each tertile.
‡Odds ratio associated with moving one tertile. Lowest ability taken as baseline odds.

Table 3: **Association between IQ score* at ages 8, 11, and 15 years and later schizophrenia**

Subset of Pintner inventory*	Population distribution of Pintner score†			Test for linear trend in odds ratio
	Lowest tertile	Middle tertile	Highest tertile	
Sociability				
Number of cases	14	6	4	
Adjusted odds ratio	1	0 8 (0 3–2 2)	0 3 (0 1–1 0)	p=0 04
Aggression				
Number of cases	11	6	6	
Adjusted odds ratio	1	0 8 (0 3–2 4)	0 5 (0 2–1 6)	p=0 2
Emotional stability				
Number of cases	9	7	9	.
Adjusted odds ratio	1	1 1 (0 4–3 3)	1 2 (0 4–3 3)	p=0 8
Attitudes to others				
Number of cases	8	9	8	..
Adjusted odds ratio	1	1 0 (0 3–2 9)	1 1 (0 3–3 4)	p=0 9

*For sociability, high = sociable; aggression, low = peaceful; emotional stability, high = abnormal; attitudes, high = negative. †One-third of controls in each group.

Table 4: **Association between self-reported personality ratings at age 13 (Pintner Inventory) and later schizophrenia**

independent of scores at 8 and 11 (odds ratio for linear trend 0·64, p = 0·04).

Social and behavioural characteristics

Solitary play preference at ages 4 and 6 years was associated with later schizophrenia (age 4, odds ratio 2·1 [0·9–4·7], p = 0·05; age 6, 2·5 [0·8–6·9], p = 0·05). At age 13, the extent of self-reported anxiety in social situations showed a linear association with risk of later schizophrenia (table 4). there was a complementary, non-significant trend for low aggression but no evidence of any effect for emotional stability or negative attitudes to others.

When the cohort members were 15 years old (table 5), teachers rated the future cases as more anxious in school. As at age 13, there was evidence of a linear trend in risk; the more anxious children were, the more likely they were to develop schizophrenia. There was no association with antisocial behaviour. Twitches, grimaces, and nail-biting seemed more common in cases. There was no evidence of effect modification by sex at 13 or 15 years. At 15, anxiety (odds ratio 1·3, p < 0·001) and the IQ score (0·5, p = 0·009) were statistically independent predictors of schizophrenia.

Missing data and misclassification bias

The average proportion of survey members with missing data at any age was similar for cases (14%) and controls (17%), as were the proportions of boys and girls. Associations were examined with and without the cases in the less confident diagnostic category. No differences in the patterns of odds ratios were noted, and the magnitude of the associations was virtually unchanged.

Subset of teacher ratings*	Population distribution of teachers' ratings†			Test for linear trend in odds ratio
	Lowest tertile	Middle tertile	Highest tertile	
Anxious behaviour				
Number of cases	3	6	11	.
Adjusted odds ratio	1 0	2 0 (0 5–10 3)	5 6 (1 4–24)	p=0 003
Antisocial behaviour				
Number of cases	9	3	11	..
Adjusted odds ratio	1 0	0 5 (0 1–1 8)	1 3 (0 5–3 7)	p=0 4
Habit behaviours‡				
Number of cases	15	6	1	..
Number of controls	3081	786	13	..
Adjusted odds ratio	1 0	1 5 (0 8–2 1)	17 1 (0 7–159)	..

*High scores indicate anxious, antisocial, and abnormal behaviours.
†One third of controls in each group.
‡Not normally distributed: 0, 1–3, 4–6.

Table 5: **Association between factors derived from teachers' ratings of behaviour at age 15 and later schizophrenia**

Discussion

This investigation in a national birth cohort found associations between various childhood developmental characteristics and adult-onset schizophrenia. Some effects were subtle; no child destined to develop schizophrenia could be singled out as a late walker or as having learning difficulties, for example. Investigations in this cohort[21,23] into childhood factors predicting affective and neurotic symptoms at age 36 identified mainly social factors, not educational achievement or neurodevelopmental features, which suggested some degree of specificity for our findings in this study, at least to psychosis.

Limited statistical power hindered interpretation of negative findings and emphasis was placed on patterns of results and linear trends in associations. In this context, the confirmation in a general population sample of previously demonstrated associations was all the more convincing. Several independent sources of case ascertainment led to greater validity and general relevance than would have been achieved from only routine follow-up data or hospital discharge diagnoses. The lack of standard diagnostic assessments at disease onset remains a limitation, but we were reassured by finding that results were similar for the cases from the two groups of diagnostic certainty.

Inclusion in the risk set of children with epilepsy and learning difficulties, known to be associated with some of the exposures of interest, was a conservative approach; any resulting bias would have reduced associations between development and schizophrenia. There was no evidence of effect modification by sex. We acknowledge the low statistical power of formal tests of interaction but noted very similar effects for boys and girls.

The risk of schizophrenia we found (0·63%) is similar to the predicted risk of 0·61% by age 40.[7] No significant sociodemographic predictors of schizophrenia emerged, although the trend appeared to be for higher social status to predict the illness, as found with the UK 1958 cohort.[7] Birth in a city was not associated with schizophrenia, although the small predicted effect[24] was beyond the statistical resolution of this study.

The finding that mothers of cases were rated as less skilled in their management and understanding of their children accords with the association between quality of rearing environment and schizophrenia in children at high genetic risk,[25] and Robins' finding[12] that many children attending child guidance clinics who went on to develop schizophrenia had been removed from their families because of neglect. However, the conclusion that quality of mothering might have a causal role in schizophrenia is not warranted. Our finding might reflect attributes of the child, who might already have deviant features, attributes of the mother, or a combination.

The evidence of aberrant speech development complements hypotheses to explain voice hallucinations and other positive phenomena on the basis of abnormal language mechanisms,[26] although the later walking and other perturbations of motor development suggests that any underlying developmental abnormality is not specific. Cases did not show grossly abnormal speech or motor behaviour in adolescence; they had apparently caught up, although the excess motor habits at age 15 years may represent a vestige of motor abnormalities.

Poor educational test performance preceding schizophrenia was independent of behaviour and was apparent by age 8 as a general deleterious effect, possibly increasing thereafter. Schizophrenia did not occur only within the population with lowest IQ, and there was some evidence of a linear trend in the association between test scores and the disorder. Extrapolation of our findings would predict a high frequency of schizophrenia among the minority of the population with learning difficulties.[27]

Children destined to develop schizophrenia showed continuity between 4 and 15 years, being characterised by an aloof, solitary habit with avoidance of social interaction. This impression came from mothers, teachers, and even the children themselves. The robust finding is reminiscent of the early reports of asociality and the schizoid premorbid personality.[28] There was no evidence of increased antisocial or aggressive behaviour, nor of conspicuous differences between girls and boys. Antisocial behaviour preceding schizophrenia, mainly in boys, has been reported in children attending child guidance clinics[12] where findings may be difficult to generalise, and in cohort studies, in which antisocial conduct might have been more noteworthy than on shyness.[7]

Analysis of continuous measures of IQ and behaviour provided no convincing evidence that any attributable risk of schizophrenia was confined to a subgroup of the population defined according to these factors. Linear trends of increasing risk across the population distribution suggest the possibility of a relation between position within this distribution and frequency of schizophrenia similar to that between, for example, blood pressure and stroke. These results require replication, particularly to confirm whether the associations are truly linear or are better described by a more complex equation. However, for individuals, this model accommodates the possibility of a high prevalence of covert, early decrements in those with schizophrenia, echoing findings from studies of monozygotic twins discordant for schizophrenia, in which most affected subjects differ predictably from the twin. The notion of neurodevelopmental schizophrenia as a minority subtype may have been too restrictive, perpetuated by the classification of early events as either normal or abnormal, a strategy that may mask quite large effects in the majority of affected subjects who remain, nevertheless, within the normal range.

This view of attenuated development before the clinical syndrome of schizophrenia is quite compatible with aetiological heterogeneity. Our results suggest initial events early in life but do not exclude a dynamic process over a long time. The development of fine structure and function are mutually dependent in the immature brain. Various factors might initiate a self-perpetuating cascade of progressively more abnormal function, culminating in the emergence of psychosis, either in a time-dependent but not necessarily linear manner, or after further, necessary events. Such a developmental model, extending the notion of a static, localised lesion with changing manifestation,[29] is compatible with the rarity of schizophrenia in childhood, its characteristic distribution of incidence in young adulthood, and perhaps with the eventual possibility of intervention. Re-formulating the question regarding childhood antecedents of schizophrenia from a qualitative to a quantitative one,[30] this model, can be tested by attention to continuous measures in other longitudinal data.

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Short reports

Transplantation of porcine fetal pancreas to diabetic patients

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Transplanation of fetal porcine islet-like cell clusters (ICC) reverses diabetes in experimental animals. We have now transplanted porcine ICC to ten insulin-dependent diabetic kidney-transplant patients. All patients received standard immunosuppression and, at ICC transplantation, antithymocyte globulin or 15-deoxyspergualin. ICC were injected intraportally or placed under the kidney capsule of the renal graft. Four patients excreted small amounts of porcine C-peptide in urine for 200–400 days. In one renal-graft biopsy specimen, morphologically intact epithelial cells stained positively for insulin and glucagon in the subcapsular space. We conclude that porcine pancreatic endocrine tissue can survive in the human body.

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Some patients have become temporarily insulin-independent after transplantation of human pancreatic islets. If islet transplantation is to become routine practice, the supply of human pancreases will be insufficient. Since porcine insulin adequately substitutes for human insulin, pig islets might be an alternative. After transplantation of islet-like cell clusters (ICC) from fetal pig pancreases into 1 diabetic nude mice, most cells differentiated into β-cells[1] and normoglycaemia followed.[2] Although human natural porcine antibodies bind to the ICC, they do not kill the porcine cells.[3] Transmission of identifiable infectious agents can also be avoided.[4] Intraportal injection of the porcine ICC to dogs resulted in no adverse effects.[5] In view of these findings, we did a pilot trial of transplantation of porcine ICC into diabetic patients.

Pancreatic tissue was obtained from pig fetuses (Swedish land race), gestational age 66–81 days (full-term is 120 days). For a single transplantation, pancreases from 39–100 fetuses (4–8 litters) were used. After slaughter of the sow in the hospital, the uterus was removed under sterile conditions and placed on ice. The preparation of ICC has been described.[1,6] The average yield from a fetus was about 10 000 ICC. Approval for the trial was obtained from the human ethics committee at the Karolinska Institute.

The ten recipients had type 1 diabetes mellitus and end-stage diabetic nephropathy. There were nine women and one man aged 30–47 years (mean 40); duration of diabetes was 21–40 years (mean 30). After an arginine stimulation test, none of the patients had any C-peptides in serum. Six patients had undergone cadaveric and two had undergone living-related renal transplantation 2–17 years earlier. These patients were given the